Supplementary Online Content

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

eMethods 1. Sample acquisition and pre-test sample processing.

Once determined by the ordering physician that the patient's presentation is clinically appropriate for CES, patients were offered the test after a counseling session ("pre-test counseling") [eFigure 1]. If the patient agreed to the CES test, a whole blood sample was collected in an EDTA or lavender top tube and sent to the UCLA Molecular Diagnostics Laboratories. Only blood samples collected within 96 hours prior to arrival in the laboratory were accepted. High molecular weight genomic DNA samples extracted in an outside facility were also accepted when whole blood samples were unavailable or difficult to obtain (such as those from international patients). The minimum required amount of genomic DNA was 10ug at 100ng/µl, preferably accompanied with the 1-2% agarose gel run image and 260/280 ratio. Other specimen types were not acceptable (except for the cases where whole blood samples were not available such as terminated fetuses). Genomic DNA was either extracted using standard methods (QIAcube Qiagen, Valencia, CA) and was run on 1% agarose gel to check for degradation and measured by both Nanodrop and Qubit (Life Technologies).

eMethods 2. Exome capture and sequencing.

Library preparation, sequencing and data analysis were performed at the UCLA Clinical Genomics Center using CLIA (Clinical Laboratory Improvement Amendments) and CAP (College of American Pathologists) validated protocols [eFigure 1]. For the Trio CES cases where the three samples were not received at the same time, the DNA was extracted upon receipt but the library preparation and sequencing were put on hold until all three samples were received to minimize batch effects. As described in Strom et al.[1], multiple steps including checking the inheritance status in the trios and comparing to previous genetic test results are taken to reduce the probability of sample swap errors. Three µg of high molecular weight genomic DNA (as measured by Qubit) from each participant was subjected to library preparation and exome capture following the customized Agilent SureSelect Human All Exon V2 50Mb Illumina Paired-End Sequencing Library Prep Protocol. Sequencing was performed on an Illumina HiSeq2000 or HiSeq2500 as a 50bp or 100bp paired-end run, respectively. For each sample, approximately 60 million independent paired reads were generated.

eMethods 3. Sequence data analysis.

The sequence data were aligned to the GRCh37 human reference genome using Novoalign (Novocraft, http://www.novocraft.com/main/index.php) V2.07.15b. PCR duplicates were marked using Picard-tools-1.42 (http://picard.sourceforge.net/) [eFigure1]. GATK[2,3] v1.1-33 was used for INDEL (insertions and deletions) realignment and base quality recalibration. Both SNVs (single nucleotide variants) and small INDELs within the coding regions +/-2bp were called using GATK unified genotyper. SNVs were recalibrated using GATK Variant Quality Score Recalibration (VQSR) tool and INDELs were filtered using GATK INDEL filtration tool. Variants were evaluated using GATK VariantEval tool and all variants were annotated using Variant Annotator X (VAX)[4]. GATK DepthOfCoverage tool was used to calculate depth of coverage for each chromosomal arm, chromosome X, Y and MT, genome and exome. Linkdatagen (http://bioinf.wehi.edu.au/software/linkdatagen/)[5,6] and PLINK (http://pngu.mgh.harvard.edu/~purcell/plink/)[7] were used to determined regions of homozygosity by descent (ROH).

eMethods 4. Variant filtration and interpretation.

Annotated variants were deposited into MySQL 5.2 database for filtering [eFigure 1 and 2]. First step of variant filtration was selecting only the variants that result in amino acid alteration in any of the transcripts. Second step of variant filtration was filtering out common variants with minor allele frequency (MAF) of 1%. MAF was estimated using a combined dataset incorporating all available data from the 1000 genomes project (1Kg), NHLBI exome sequencing project (ESP), NIEHS environmental genome project (EGP) and HapMap, without the distinction of ethnic background. Any variant not observed in any of these datasets was considered "novel" for future analysis.

Then, for the trio-CES cases, variants were further filtered into 4 categories [eFigure 2]: *de novo* variants, homozygous variants, compound heterozygous (CH) variants and inherited heterozygous variants. There were 0-3 high quality *de novo* amino acid altering novel variants where the proband is heterozygous and the parents and >50 samples analyzed in the same batch are unambiguously (no indication of the variant allele being present) homozygous for the reference allele with >10X coverage, ≥500 QUAL score, and marked as PASS filters by GATK VariantEval. For non-consanguineous families, there were <10 homozygous variants that are not homozygous in the parents and <10 genes with CH variants (one variant inherited from the father and the other variant inherited from the mother). Rest of the variants would have been inherited from either of the parents. For proband-CES cases, it was not possible to deduce *de novo* or CH variants, so ~600 heterozygous and <10 homozygous variants were subject for primary interpretation.

First step of interpretation was intersecting the genotype data with the phenotype information of the patient. To achieve that, first a list of phenotypic keywords was generated by extracting clinical information from the clinical notes submitted by the ordering physician. If any genetic testing was done prior to ordering CES, the reports or the results from those testing was highly recommended for submission as these information was not only useful to confirm that CES also replicates the findings, if there were any, and also guided the interpretation by giving better idea which differential diagnoses were considered. From the phenotypic keyword list, a

permissive primary gene-list (PGL) was generated by entering each keyword as a search term in the Human Gene Mutation Database Professional version (HGMD) and Online Mendelian Inheritance in Man (OMIM) database, then compiling the results to create a list of all unique gene names returned by either or both databases. Then, the PGL and the filtered variants were intersected.

For proband-CES cases, all homozygous variants, potential compound heterozygous variants (defined as genes with >1 variant locus per individual) and heterozygous variants with MAF<0.1% that are found within the PGL were equally weighed and carefully curated by the bioinformaticians [eFigure 2]. MAF 0.1% cutoff for autosomal dominant disorder is a commonly accepted threshold.[8] Heterozygous variants with MAF<1% identified in genes known to cause recessive disorders that fit the patient's phenotype well were highlighted for review at the Genomic Data Board (GDB) meeting. For trio-CES cases, all *de novo*, homozygous CH variants (regardless PGL status) were curated, and candidate variants were highlighted for review at the GDB meeting based on phenotypic correlation [eFigure 2]. Inherited heterozygous variants found in PGL that were annotated as pathogenic by HGMD or ClinVar (ww.ncbi.nlm.nih.gov/clinvar/) were equally weighed as well.

eMethods 5. Determination of variant pathogenicity

All the highlighted variants for each CES case were presented to the GDB. Determining which variants to report and how to determine their pathogenicity was done according to current ACMG sequence interpretation guidelines [eFigure 3].

For each gene with at least one highlighted variant, the patient's phenotype, the patient's variant(s), the clinical conditions associated that gene, the mode of inheritance associated with disease, and the variants classes (e.g. missense, truncating, repeat expansion) in the gene that are disease-associated were considered by the GDB. Correlation between variant type(s) and the mode(s) of inheritance associated with relevant genetic conditions were considered according to the following criteria:

Mode of inheritance	**Variant types**
Autosomal Recessive	Homozygous Compound heterozygous (trio-CES) Potential compound heterozygous in PGL (proband-CES, duo-CES*)
Autosomal Dominant	Heterozygous inherited from affected parent (trio-CES, duo-CES) Heterozygous in PGL (proband-CES)
Sporadic	*De Novo* (trio-CES) Heterozygous not inherited from parent (duo-CES) Potential *de novo*: heterozygous novel in PGL (proband-CES)
X-linked recessive	Hemizygous (males) Homozygous X-linked (females) Compound heterozygous (females, trio-CES and duo-CES, father must be potentially affected)
X-linked dominant	Heterozygous X-linked (females) inherited from affected parent (trio-CES and duo-CES) Heterozygous X-linked novel in PGL (females)
Mitochondrial	MT-DNA variants only

*Duo-CES is part of other-CES where only one parent was available for testing.

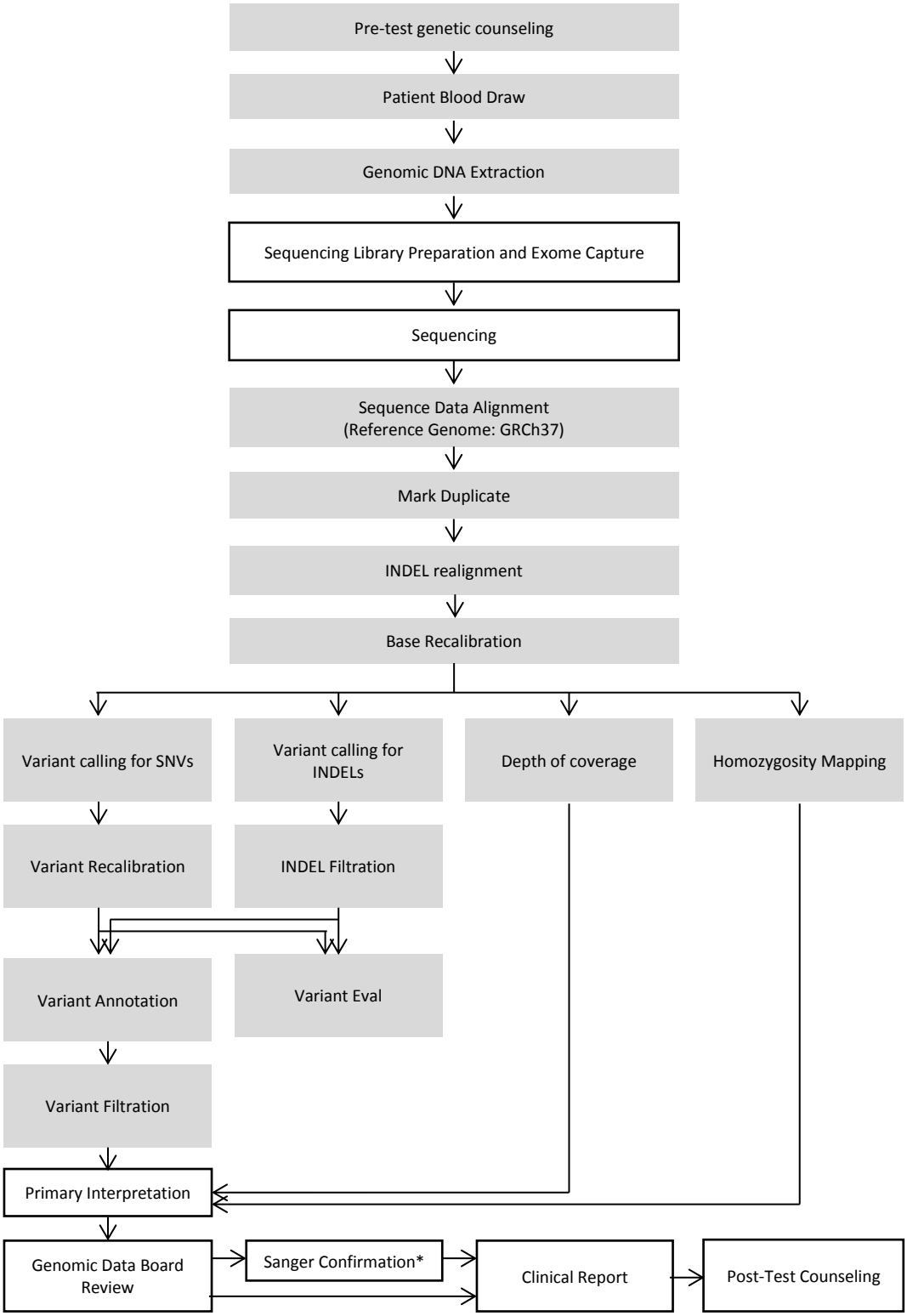
If both the phenotype and mode of inheritance were found to be consistent with the observed variant(s) by the GDB, and if the variant was deemed to be a known pathogenic variant after literature review, we reported the variant as Pathogenic. If the variant has not been published as pathogenic, we would search all known variants in the gene to check the variant type (i.e. missense, early-termination, gross deletion or duplication, splice defect) and examine if the type of variant identified is similar to the type of known variants or overlaps a known variant. If so, we reported the variants as Likely Pathogenic. If not, other information such as gene-wise rare variant burden in the general population and gene-wise rare variant burden in internal data were considered by the GDB to estimate whether the variant(s) meet criteria as likely pathogenic. An illustrative example of the importance of gene-wise rare variant burden is the titin gene *TTN*, which is known to have a very high rare variant burden[9]. Novel missense variants in *TTN* are typically not reported, while truncating variants were reported as likely pathogenic heterozygous (patient #180 in eTable 2) or pathogenic (if homozygous or compound heterozygous).

For proband-CES cases with more than one heterozygous variant in a recessive gene, we reported the variants as likely pathogenic rather than pathogenic to account for the uncertain phase (i.e. whether the variants are in *cis* or *trans*). In cases where the patient appeared to be a carrier of a single pathogenic or likely pathogenic heterozygous variant in a gene causing an autosomal recessive disorder, we reported the variant as a VUS along with gene coverage information and recommended further testing. When a variant was found within a gene that could fit the patient's clinical presentation but not perfectly matched, we reported a known variant as Likely Pathogenic when we the inheritance mode fit and as VUS when the inheritance mode of the variant was unknown. If the variant was not a known variant, the same questions for variant type and mutational burden for the gene were asked to determine the pathogenicity.

If a variant did not meet the above listed criteria but was determined by the GDB to be relevant to the care and management of the patient's primary clinical concerns, it was reported at as a variant of uncertain clinical significance (VUS).

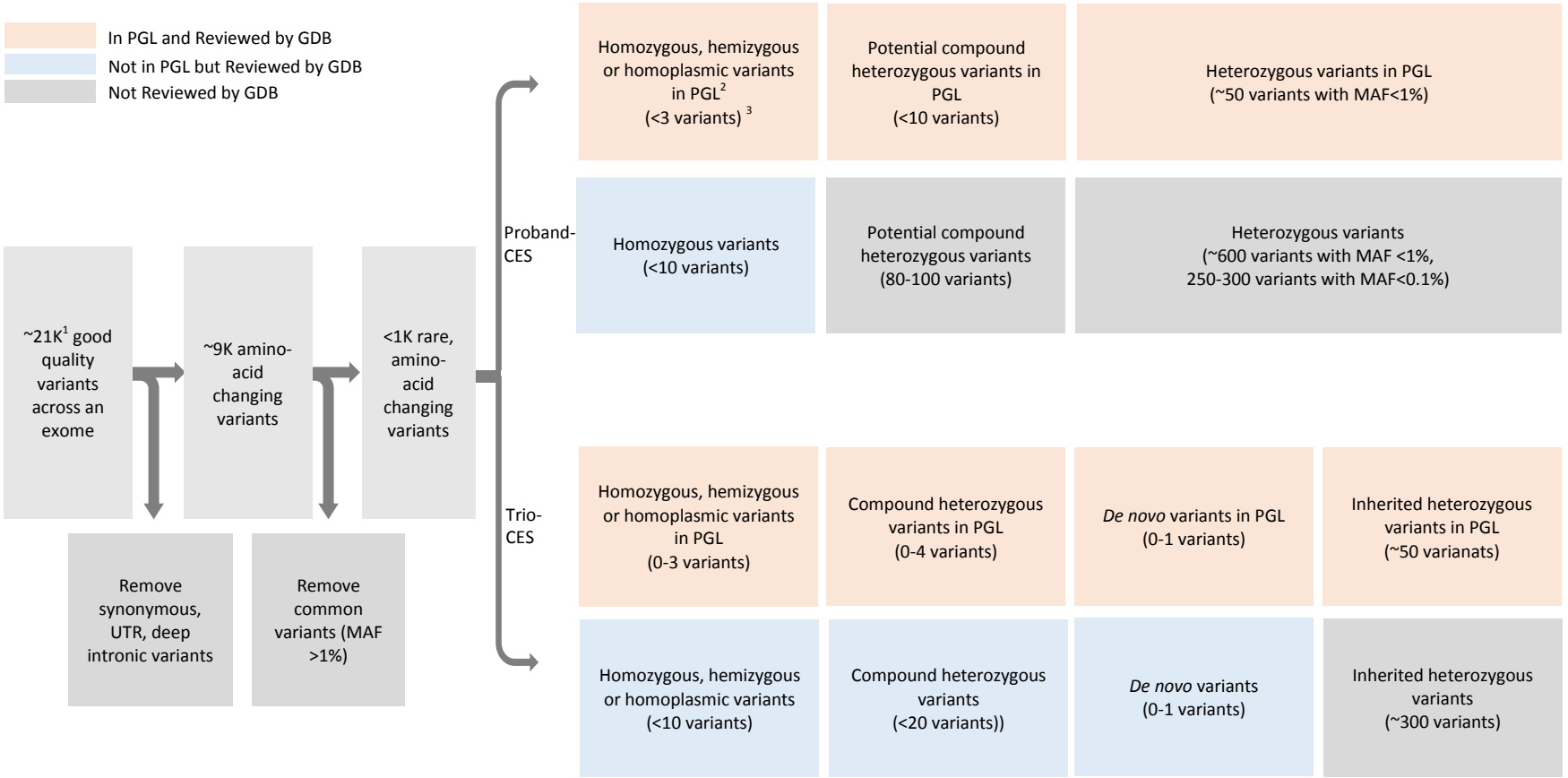
For cases reviewed prior to July 1, 2013 (over 300 cases), all reported variants were confirmed by Sanger sequencing as an alternate methodology, with a confirmation rate >99%. After empirically determining that SNVs with QUAL score >=500 are highly accurate[1], routine confirmation of such variants was stopped for cases reviewed after July 1, 2013 (>250 cases to date). Confirmation of low quality SNVs and all small insertion/deletion variants identified by CES (approximately 20% of reported variants) are still routinely confirmed by Sanger sequencing. On rare occasions, when attempting to confirm low quality SNVs or insertion/deletion variants, PCR amplification failed using two unique primer sets. For these variants, cases were signed-out with a note indicating that confirmation was not possible within the confines of CES testing with a recommendation to seek confirmation by an outside laboratory.

eFigure 1. UCLA Clinical Exome Sequencing (CES) workflow.



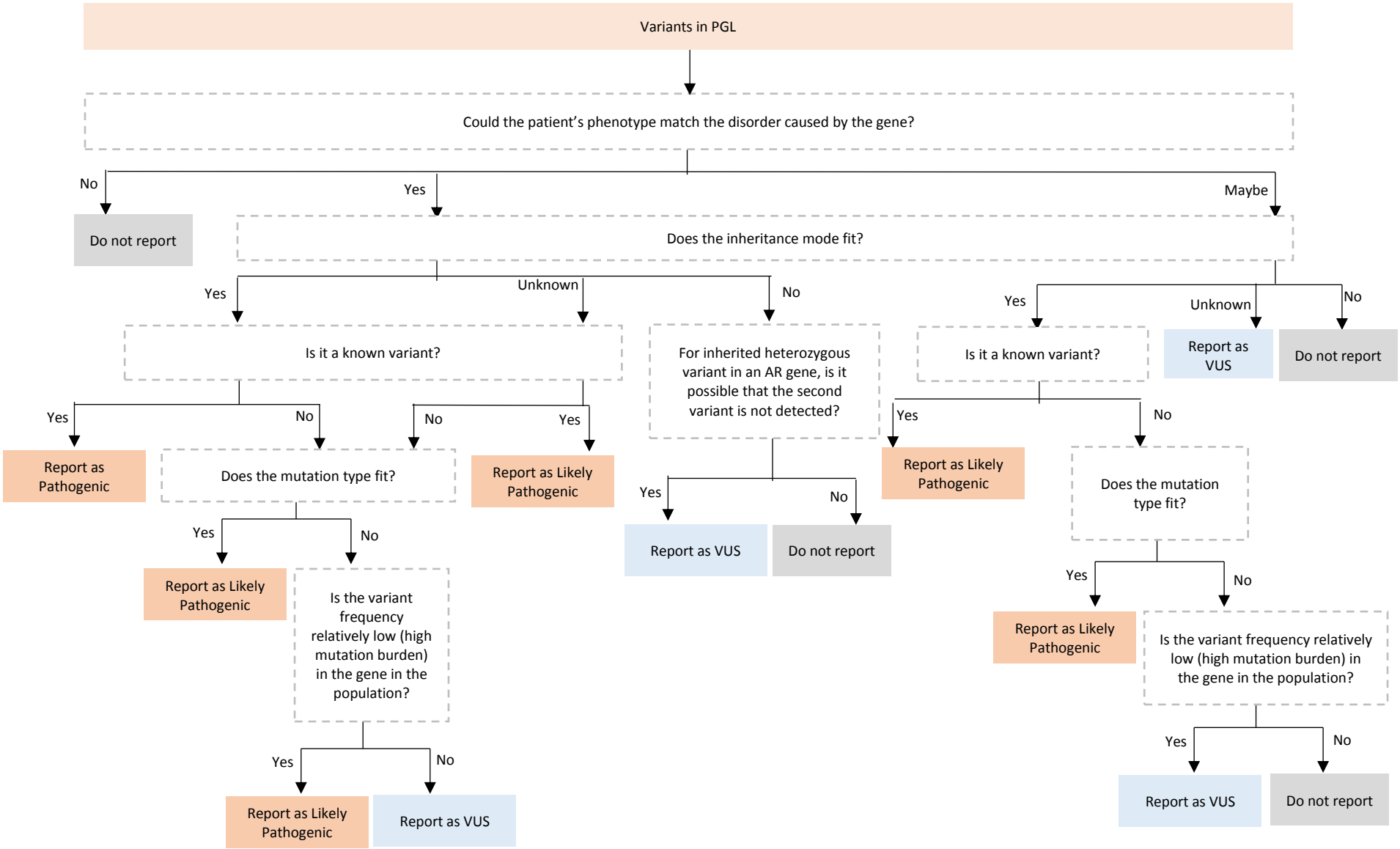
*Sanger confirmation was only performed on SNVs with QUAL score <500 or flagged as Tranched by GATK VQSR and all small INDELs.

eFigure 2. Variant filtration workflow starting with ~21K variants across the exome and comparing the approximate number of variants observed from trio-CES versus proband-CES.



[1] European Caucasian sample.
[2] Primary genelist (PGL): Number of variants identified in PGL varied by the size of the PGL. Numbers in this figure were generated assuming the PGL contained ~1000 genes.
[3] Non-consanguineous sample.

eFigure 3. Variant classification workflow for the variants found within the primary genelist (PGL).



eTable 1. Metrics used to determine the adequate quality of the sequencing test for each sample: total number of single nucleotide variants (SNVs) called, percentage of those SNVs found in dbSNP132 (i.e. known variants), concordance rate of the called non-reference variant at dbSNP positions with the known alternate variants, transition to transversion (Ti/Tv) ratio, heterozygous/homozygous ratio, and total number of small insertions and deletions (indels, <10bp) found. Mean and standard deviation of each metric is shown and samples are divided into non-African American and African American, as African Americans have a substantially higher number of variants than non-African Americans due to their higher diversity[10].

Metrics	Mean (Standard Deviation)		
	All (n=1,734)	**Non-African American (n=1,662)**	**African American (n=72)**
Total No. SNVs	21,278 (859)	24,789 (919)	21,126 (419)
% of SNVs found in dbSNP132 (known)	96.5% (0.6)	95.2% (0.5)	96.5% (0.6)
Concordance rate of the known variants	99.9% (0)	99.9% (0)	99.9% (0)
Known variants			
Ti/Tv ratio	3.15 (0.04)	3.18 (0.03)	3.15 (0.04)
Het/Homo ratio	1.46 (0.14)	1.85 (0.14)	1.44 (0.12)
Novel variants			
Ti/Tv ratio	2.75 (0.25)	2.73 (0.16)	2.75 (0.25)
Het/Homo ratio	18.81 (5.95)	25.18 (8.78)	18.54 (5.64)
Total No. of INDELs	1385 (163)	1487 (176)	1381 (161)

eTable 2. List of molecular diagnoses made. (P: Pathogenic, LP: Likely pathogenic, VUS: Variant of uncertain significance, U: Unknown, M: Mother, F: Father)

Patient Index	Age	Gene Name	Protein Change	Variant Class	Inherited From	Disease Name	Clinical Indication*
Proband-CES Homozygous							
1	8	*CLN8*	p.Arg204Cys	LP	U	ceroid-lipofuscinosis, neuronal 8 [MIM: 600143]	infantile neuroaxonal dystrophy, developmental deterioration, seizure
2	10	*AHI1*	p.Glu1086Gly	LP	U	autosomal recessive Joubert syndrome 3 [MIM: 608629]	ataxia, motor delay, cognitive delay, cataracts, oral facial dystonia, cerebellar atrophy, midbrain atrophy, brain atrophy, hypotonia, spasticity, inversion of feet, cerebellar degeneration
3	37	*USH2A*	p.Cys759Phe	LP	U	autosomal recessive Retinitis Pigmentosa type 39 [MIM: 613809]	retinitis pigmentosa, nyctalopia, night blindness, vision loss, intraretinal pigmentation
4	50	*CRB1*	p.Val743Leu	LP	U	autosomal recessive retinitis pigmentosa type 12 [MIM: 600105]	retinitis pigmentosa, helicoid dystrophy, macular edema, retinal dystrophy
5	57	*SYNE1*	Splice Defect	LP	U	autosomal recessive spinocerebellar ataxia type 8 (SCAR8) [MIM: 610743]	Pure cerebellar ataxia, cerebellar atrophy
6	1	*CDK5RAP2*	p.Arg1481*	LP	U	autosomal recessive primary microcephaly type 3 [MIM: 604804]	Agenesis of corpus callosum, constipation, dysmorphic features, hearing loss, hoarse voice, holoprosencephaly, hypotelorism, interhemispheric cyst, lissencephaly, microcephaly, pachygyria, speech delay
7	26	*SPG7*	p.Gly577Ser	LP	U	autosomal recessive Spastic Paraplegia type 7 [MIM: 607259]	Cerebellar atrophy, Brainstem atrophy, deafness, ataxia, Hyper-reflexia, Hyperreflexia
8	39	*RPGRIP1*	p.Asp966Ilefs	LP	U	autosomal recessive cone-rod dystrophy 13 [MIM: 608194]	blurred vision, rod-cone dystrophy, retinitis pigmentosa, nystagmus, color disturbance, retinal pigment epithelium atrophy, pigment clump, Leber Congenital Amaurosis
9	16	*GMPPB*	p.Arg185Cys	P	U	Muscular dystrophy-dystroglycanopathy (congenital with brain and eye anomalies), type A, 14 [MIM: 615350]; Muscular dystrophy-dystroglycanopathy (congenital with mental retardation), type B, 14 [MIM: 615351]; Muscular dystrophy-dystroglycanopathy (limb-girdle), type C, 14 [MIM: 615352]	muscle weakness, muscular dystrophy, asthenic build, cataracts, dysmorphic features, short stature, learning disability, Marinesco-Sjogren syndrome, scoliosis, arachnodactyly, Camptodactyly, dystroglycanopathy, laminopathy, arthrogryposis
10	16	*DCAF17*	p.Ile97Asnfs*22	P	U	autosomal recessive Woodhouse-	developmental delay, short stature,

Patient Index	Age	Gene Name	Protein Change	Variant Class	Inherited From	Disease Name	Clinical Indication*
						Sakati Syndrome [MIM: 241080]	microcephaly, small pituitary, hypopituitarism, delayed puberty, small testes, low IGF1, hyperreflexia, gait problem
11	62	*GBE1*	p.Tyr329Ser	P	U	autosomal recessive adult polyglucosan body disease [MIM: 263570]; glycogen storage disease type IV [MIM: 232500]	Leukodystrophy, White matter, Ataxia, Neuropathy
Hemizygous							
12	12	*DMD*	p.Gly1334*	LP	U	Duchenne muscular dystrophy (DMD) [MIM: 310200]	autism, hyper-Ckemia, muscular dystrophy, dystrophin, cardiomyopathy, rhabdomyolysis
13	36	*G6PD*	p.Ser188Phe	LP	U	X-linked chronic non-spherocytic hemolytic anemia due to G6PD deficiency [MIM: 305900]	G6PD deficiency, spasticity, Upper motor neuron, Dysgraphia, Learning disability, Spinal cord atrophy, White matter changes, Leukodystrophy, Vitamin E deficiency, Abnormal liver function
Potential Compound Heterozygous							
14	27	*TTN*	p.Asp17434Gly	LP	U	Cardiomyopathy, dilated, 1G [MIM: 604145]; Cardiomyopathy, familial hypertrophic, 9 [MIM: 613765]	marfan, mitral, mitral valve prolapse, atrial fibrillation, cardiomyopathy, connective tissue disorder
14	27	*TTN*	p.Cys12844*	LP	U	Cardiomyopathy, dilated, 1G [MIM: 604145]; Cardiomyopathy, familial hypertrophic, 9 [MIM: 613765]	marfan, mitral, mitral valve prolapse, atrial fibrillation, cardiomyopathy, connective tissue disorder
15	44	*SYNE1*	Splice defect	LP	U	SYNE1-related autosomal recessive cerebellar ataxia (also known as autosomal recessive cerebellar ataxia type 1 or ARCA1) [MIM: 610743]	cerebellar ataxia
15	44	*SYNE1*	p.Lys3216*	LP	U	SYNE1-related autosomal recessive cerebellar ataxia (also known as autosomal recessive cerebellar ataxia type 1 or ARCA1) [MIM: 610743]	cerebellar ataxia
16	48	*SYNE1*	p.Trp2646*	LP	U	SYNE1-related autosomal recessive cerebellar ataxia (also known as autosomal recessive cerebellar ataxia type 1 or ARCA1) [MIM: 610743]	Ataxia, CoQ10 Deficiency, mitochondrial disorder, cerebellar atrophy
16	48	*SYNE1*	p.Arg6684*	LP	U	SYNE1-related autosomal recessive cerebellar ataxia (also known as autosomal recessive cerebellar ataxia	Ataxia, CoQ10 Deficiency, mitochondrial disorder, cerebellar atrophy

Patient Index	Age	Gene Name	Protein Change	Variant Class	Inherited From	Disease Name	Clinical Indication*
						type 1 or ARCA1) [MIM: 610743]	
17	6	*ITGA2B*	p.Leu147Val	P	U	autosomal recessive Glanzmann thrombasthenia [MIM: 273800]	bruising, von Willebran disease, thrombocytopenia, platelet disorder
17	6	*ITGA2B*	p.Ile596Thr	P	U	autosomal recessive Glanzmann thrombasthenia [MIM: 273800]	bruising, von Willebrand disease, thrombocytopenia, platelet disorder
18	18	*ATP7B*	p.Asn1270Ser	P	U	autosomal recessive Wilson Disease [MIM:277900]	Wilson disease, liver transplantation, thrombus, pyelonephritis, hemoperitoneum, pancreatitis
18	18	*ATP7B*	p.Pro984Ala	LP	U	autosomal recessive Wilson Disease [MIM:277900]	Wilson disease, liver transplantation, thrombus, pyelonephritis, hemoperitoneum, pancreatitis
19	57	*ABCA4*	p.Gly863Ala	P	U	autosomal recessive Stargardt Disease [MIM: 248200]	macular dystrophy, foveal dystrophy, pattern dystrophy, Stargardt, macular degeneration
19	57	*ABCA4*	p.Gly1961Glu	P	U	autosomal recessive Stargardt Disease [MIM: 248200]	macular dystrophy, foveal dystrophy, pattern dystrophy, Stargardt, macular degeneration
20	0	*HSD17B3*	p.Ser65Leu	LP	U	autosomal recessive 17-beta hydroxysteroid dehydrogenase III deficiency (a.k.a. male pseudohermaphroditism with gynecomastia) [MIM: 264300]	46 XY, bilateral hernias, palpable gonads, androgen insensitivity syndrome
20	0	*HSD17B3*	p.Arg80Gln	LP	U	autosomal recessive 17-beta hydroxysteroid dehydrogenase III deficiency (a.k.a. male pseudohermaphroditism with gynecomastia) [MIM: 264300]	46 XY, bilateral hernias, palpable gonads, androgen insensitivity syndrome
21	2	*ADA*	p.Ala329Val	LP	U	Severe combined immunodeficiency due to ADA deficiency [MIM: 102700]	adenosine deaminase deficiency, hepatosplenomegaly, immunodeficiency, pancytopenia, SCID
21	2	*ADA*	Splice defect	LP	U	Severe combined immunodeficiency due to ADA deficiency [MIM: 102700]	adenosine deaminase deficiency, hepatosplenomegaly, immunodeficiency, pancytopenia, SCID
22	51	*SPG7*	p.Ala510Val	LP	U	autosomal recessive spastic paraplegia type 7 [MIM: 607259]	Hyper reflexia, leukodystrophy, neuropathy, spasticity, spasticity, white matter
22	51	*SPG7*	p.Ala708Lysfs	LP	U	autosomal recessive spastic paraplegia type 7 [MIM: 607259]	Hyper reflexia, leukodystrophy, neuropathy, spasticity, spasticity, white matter
23	19	*DYSF*	p.Ser1173*	LP	U	autosomal recessive Miyoshi muscular dystrophy-1 [MIM: 254130]; autosomal recessive limb-girdle muscular dystrophy type 2B [MIM: 253601]; distal myopathy with	muscle weakness, numbness, fatigue, Myalgia, calf pain , central nucleation, myotonic dystrophy, muscular dystrophy, chest pain, asthma, loss of consciousness

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						anterior tibial onset [MIM: 606768]	
23	19	*DYSF*	p.Arg1693Gln	LP	U	autosomal recessive Miyoshi muscular dystrophy-1 [MIM: 254130]; autosomal recessive limb-girdle muscular dystrophy type 2B [MIM: 253601]; distal myopathy with anterior tibial onset [MIM: 606768]	muscle weakness, numbness, fatigue, Myalgia, calf pain , central nucleation, myotonic dystrophy, muscular dystrophy, chest pain, asthma, loss of consciousness
24	35	*ANO5*	p.Asn52Ser	LP	U	autosomal recessive limb-girdle muscular dystrophy type 2L [MIM: 611397]	myopathy, muscle aches, myalgia
24	35	*ANO5*	p.Asn64Lys*15	LP	U	autosomal recessive limb-girdle muscular dystrophy type 2L [MIM: 611397]	myopathy, muscle aches, myalgia
25	29	*RYR1*	p.Arg2241*	LP	U	autosomal recessive congenital neuromuscular disease; central core disease [MIM: 117000]	muscular dystrophy, myopathy, muscle weakness, central core disease, minicore disease
25	29	*RYR1*	p.Asp708Asn	V	U	autosomal recessive congenital neuromuscular disease; central core disease [MIM: 117000]	muscular dystrophy, myopathy, muscle weakness, central core disease, minicore disease
25	29	*RYR1*	p.Arg1999Cys	V	U	autosomal recessive congenital neuromuscular disease; central core disease [MIM: 117000]	muscular dystrophy, myopathy, muscle weakness, central core disease, minicore disease
26	59	*DYSF*	Splice defect	LP	U	limb-girdle muscular dystrophy type 2B [MIM: 253601]	muscular dystrophy, muscle weakness, muscular atrophy, muscle atrophy
26	59	*DYSF*	p.Lys1526Thr	LP	U	limb-girdle muscular dystrophy type 2B [MIM: 253601]	muscular dystrophy, muscle weakness, muscular atrophy, muscle atrophy
27	36	*MRE11A*	p.Pro166Leu	LP	U	autosomal recessive ataxia-telangiectasia-like disorder [MIM: 604391]	Ataxia, developmental delay, oculomotor apraxia, involuntary movements, chorea, myoclonus
27	36	*MRE11A*	p.Leu56Phe	LP	U	autosomal recessive ataxia-telangiectasia-like disorder [MIM: 604391]	Ataxia, developmental delay, oculomotor apraxia, involuntary movements, chorea, myoclonus
28	4	*DOK7*	p.Ser422Hisfs*34	LP	U	autosomal recessive fetal akinesia deformation sequence [MIM: 208150]; familial limb-girdle myasthenia [MIM: 254300]	muscle weakness, ptosis, gross motor delays, myopathy, hypotonia, muscular dystrophy
28	4	*DOK7*	p.Ser422Leufs*97	LP	U	autosomal recessive fetal akinesia deformation sequence [MIM: 208150]; familial limb-girdle myasthenia [MIM: 254300]	muscle weakness, ptosis, gross motor delays, myopathy, hypotonia, muscular dystrophy
29	54	*DOK7*	Splice defect	P	U	autosomal recessive familial limb-	muscle weakness, myopathy, muscular

Patient Index	Age	Gene Name	Protein Change	Variant Class	Inherited From	Disease Name	Clinical Indication*
						girdle myasthenia [MIM: 254300]	dystrophy, orthopnea, dyspnea on exertion, dysarthria, myasthenia gravis
29	54	*DOK7*	p.Ala378Serfs*30	P	U	autosomal recessive familial limb-girdle myasthenia [MIM: 254300]	muscle weakness, myopathy, muscular dystrophy, orthopnea, dyspnea on exertion, dysarthria, myasthenia gravis
30	62	*CAPN3*	p.Glu107*	P	U	autosomal recessive limb-girdle muscular dystrophy (LGMD) type 2A [MIM: 253600]	muscular dystrophy, muscle weakness
30	62	*CAPN3*	p.Arg440Gln	P	U	autosomal recessive limb-girdle muscular dystrophy (LGMD) type 2A [MIM: 253600]	muscular dystrophy, muscle weakness
31	12	*CHKB*	p.Gln51*	LP	U	autosomal recessive congenital muscular dystrophy (megaconial type) [MIM: 602541]	muscular dystrophy, muscle weakness, alpha sarcoglycanopathy, developmental delay, short stature
31	12	*CHKB*	p.Glu283Lys	LP	U	autosomal recessive congenital muscular dystrophy (megaconial type) [MIM: 602541]	muscular dystrophy, muscle weakness, alpha sarcoglycanopathy, developmental delay, short stature
31	12	*CHKB*	p.Thr301Ile	V	U	autosomal recessive congenital muscular dystrophy (megaconial type) [MIM: 602541]	muscular dystrophy, muscle weakness, alpha sarcoglycanopathy, developmental delay, short stature
32	57	*POLG*	p.Gly11Asp	LP	U	Mitochondrial DNA depletion syndrome 4A (Alpers type) [MIM: 203700]; Mitochondrial DNA depletion syndrome 4B (MNGIE type) [MIM: 613662]; Mitochondrial recessive ataxia syndrome (includes SANDO and SCAE) [MIM: 607459]; Progressive external ophthalmoplegia, autosomal dominant [MIM: 157640]; Progressive external ophthalmoplegia, autosomal recessive [MIM: 258450]	numbness, paresthesias, neuropathy, demyelination
32	57	*POLG*	p.Arg852Cys	LP	U	Mitochondrial DNA depletion syndrome 4A (Alpers type) [MIM: 203700]; Mitochondrial DNA depletion syndrome 4B (MNGIE type) [MIM: 613662]; Mitochondrial recessive ataxia syndrome (includes SANDO and SCAE) [MIM: 607459]; Progressive external	numbness, paresthesias, neuropathy, demyelination

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						ophthalmoplegia, autosomal dominant [MIM: 157640]; Progressive external ophthalmoplegia, autosomal recessive [MIM: 258450]	
33	37	*SACS*	p.Arg3875His	LP	U	autosomal recessive spastic ataxia Charlevoix-Saguenay type (ARSACS) [MIM: 270550]	neuropathy, ataxia, myelopathy, spasticity, nystagmus, lysosomal storage disorder, very long chain fatty acid disorder, metabolic disorder, Charcot-Marie-Tooth
33	37	*SACS*	p.Arg2426*	P	U	autosomal recessive spastic ataxia Charlevoix-Saguenay type (ARSACS) [MIM: 270550]	neuropathy, ataxia, myelopathy, spasticity, nystagmus, lysosomal storage disorder, very long chain fatty acid disorder, metabolic disorder, Charcot-Marie-Tooth
34	20	*ASS1*	p.Arg307Cys	LP	U	autosomal recessive citrullinemia [MIM: 215700]	Citrullinemia, developmental delay, seizures, spasticity, tremor, ataxia
34	20	*ASS1*	see eTable 3			autosomal recessive citrullinemia [MIM: 215700]	Citrullinemia, developmental delay, seizures, spasticity, tremor, ataxia
Heterozygous							
35	73	*C1QTNF5*	p.Ser163Arg	LP	U	late onset retinal degeneration (LORD) [MIM:605670]	night blindness, central atrophy, color vision distortion, cone rod dystrophy, macular dystrophy, retinitis pigmentosa
36	0	*NOTCH1*	p.Glu794SerfsX8	LP	U	Aortic valve disease [MIM: 109730]	cardiomyopathy, atrial septal defect, ventricular septal defect, heart defect, heart failure, RASopathy, Costello syndrome, Noonan syndrome, Capillary malformation-arteriovenous malformation, Autoimmune lymphoproliferative syndrome, Hereditary Gingival fibromatosis type 1, Legius syndrome, LEOPARD syndrome, Neuro-cardio-facial-cutaneous syndromes, Neurofibromatosis type 1, pulmonic stenosis, parachute mitral valve, heart murmur, bicuspid aortic valve, bilateral pleural effusion, cardiomegaly
37	15	*MYBPC3*	Splice Defect	LP	U	dilated cardiomyopathy (DCM) [MIM: 115200]; hypertrophic cardiomyopathy (HCM) [MIM: 115197]	arrhythmia, cardiomyopathy, sudden unexplained death, cardiac arrest
38	22	*PTPN11*	p.Asn58Lys	LP	U	autosomal dominant Noonan Syndrome [MIM: 163950]	Noonan

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39	69	*SCN5A*	p.Arg523Cys	LP	U	Atrial fibrillation, familial, 10 [MIM: 614022]; Brugada syndrome 1 [MIM: 601144]; Cardiomyopathy, dilated, 1E [MIM: 601154]; Heart block, nonprogressive [MIM: 113900]; Heart block, progressive, type IA [MIM: 113900]; Long QT syndrome-3 [MIM: 603830]; Sick sinus syndrome 1 [MIM: 608567]; Ventricular fibrillation, familial, 1 [MIM: 603829]	cardiomyopathy, pulmonary hypertension, hyperlipidemia, hypertension, chronic renal insufficiency, heart failure, ventricular tachycardia, sudden cardiac death, Atrial flutter, Hyperthyroidism, Colonic polyps
40	32	*MYH7*	p.Met515Thr	LP	U	Cardiomyopathy, dilated, 1S [MIM: 613426]; Cardiomyopathy, familial hypertrophic, 1 [MIM: 192600]; Laing distal myopathy [MIM: 160500]; Left ventricular noncompaction 5 [MIM: 613426]; Myopathy, myosin storage [MIM: 608358]; Scapuloperoneal syndrome, myopathic type [MIM: 181430]	cardiomyopathy, subpleural cysts, atrial fibrillation, pleural effusion, hypotonia, hypovolemia, Syndrome of inappropriate antidiuretic hormone secretion
41	4	*BCOR*	p.Gln1337*	LP	U	oculofaciocardiodental (OFCD) syndrome [MIM: 300166]	cataracts, macrocephaly, atrial septal defect , patent ductus arteriosus, cleft palate, oculofaciocardiodental, microphthalmia, Simpson Golabi Behmel Syndrome
42	46	*MYLK*	p.Asp717Tyr	LP	U	autosomal dominant familial thoracic aortic aneurysm type 7 [MIM: 613780]	thoracic aorta aneurysms, Marfan, thoracic aortic aneurysm, dissection
43	36	*TNXB*	p.Asp2025Val	LP	U	autosomal dominant Ehlers-Danlos syndrome, hypermobility type [MIM: 130020]	joint hypermobility, joint mobility, skin elasticity, gastrointestinal, skeletal pain, Ehlers-Danlos, musculoskeletal
44	31	*MPZ*	p.Pro151Thr	LP	U	Charcot-Marie-Tooth disease, dominant intermediate D [MIM: 607791]; Charcot-Marie-Tooth disease, type 1B [MIM: 118200]; Charcot-Marie-Tooth disease, type 2I [MIM: 607677]; Charcot-Marie-Tooth disease, type 2J [MIM: 607736]; Dejerine-Sottas disease [MIM: 145900]; Neuropathy, congenital hypomyelinating [MIM: 605253]; Roussy-Levy syndrome [MIM:	neuropathy, foot drop, gait abnormality, atrophy, muscle weakness, Kennedy's disease, fasciculation, muscle twitch, anorgasmia, Charcot-Marie-Tooth

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						180800]	
45	35	*TNFRSF1A*	p.Arg121Gln	P	U	autosomal dominant familial periodic fever [MIM: 142680]	fatigue, cramp, carnitine deficiency, TNF Receptor Associated Periodic syndrome, TRAPS, shortness of breath, muscle pain, thyroid resistance, mitochondrial, periodic fever syndrome
46	55	*GIGYF2*	p.Ala793Val	LP	U	autosomal dominant Parkinson Disease type 11 [MIM: 607688]	Akathisia, bradykinesia, bulbar, cognitive decline, drooling, dystonia, emotional lability, gait freezing, mask facies, Parkinson, psychomotor, speech loss, swallowing, supranuclear palsy, vertical gaze
47	40	*TGFBR2*	p.Tyr470Asp	LP	U	autosomal dominant Loeys-Dietz syndrome [MIM: 610168, 610380]	Marfan, scoliosis, aneurysms, osteoarthritis, hypoplastic ovary, absent ovary, retinal detachment, arthritis, osteoporosis, long extremities, Loeys-Dietz syndrome
48	37	*DHTKD1*	p.Arg834*	LP	U	2-aminoadipic 2-oxoadipic aciduria [MIM: 204750]; Charcot-Marie-Tooth disease, axonal, type 2Q [MIM: 615025]	muscle cramps, muscle spasms, calf atrophy, neuropathy, charcot-marie-tooth, footdrop, diffuse sensorimotor demyelinating neuropathy
49	1	*MAP3K1*	p.Pro257Leu	LP	U	46XY sex reversal type 6 [MIM: 613762]	karyotype 46XY, sexual development, hypospadias, penoscrotal transposition, bifid scrotum, undescended testis
50	21	*GATA2*	p.Asn371Lys	LP	U	Emberger syndrome [MIM: 614038]; Immunodeficiency 21 [MIM: 614172]	pancytopenia, fanconi anemia, dyskeratosis, Shwachman-Diamond syndrome, Myelodysplastic syndrome, cancer susceptibility
51	38	*VCP*	p.Arg155Gly	LP	U	Amyotrophic lateral sclerosis 14, with or without frontotemporal dementia [MIM: 613954]; Inclusion body myopathy with early-onset Paget disease and frontotemporal dementia 1 [MIM: 167320]	muscular dystrophy, twitch, weakness, waddling gait, myopathy
52	63	*SPAST*	p.Asp542Gly	LP	U	autosomal dominant spastic paraplegia type 4 [MIM: 182601]	weakness, spinal muscular atrophy, motor neuron disease
53	46	*DNMT1*	p.Tyr511Cys	LP	U	autosomal dominant hereditary sensory neuropathy type E1 [MIM: 614116]	ataxia, hearing loss, deafness, neuropathy, dementia, spasticity, cerebellar atrophy
54	24	*SCN5A*	p.Ser1710Leu	LP	U	autosomal dominant Brugada syndrome-1 [MIM: 601144]	Cardiac arrhythmia, syncope, Brugada, vaso-vagal syndrome
55	0	*COL1A2*	p.Gly1012Ser	LP	U	autosomal dominant osteogenesis imperfecta (OI), type II [MIM:	Congenital anomalies, skeletal dysplasia, dysmorphic features, femurs, osteopenia,

Patient Index	Age	Gene Name	Protein Change	Variant Class	Inherited From	Disease Name	Clinical Indication*
						166210]; OI, type III [MIM: 259420]; OI, type IV [MIM: 166220]; autosomal dominant Ehlers-Danlos syndrome type VIIB [MIM: 130060]	oligohydramnios, osteogenesis imperfecta, diaphyseal disorder
56	14	*UBE3A*	p.Leu825Phefs*15	LP	U	autosomal dominant Angelman syndrome [MIM: 105830]	developmental delay, poor balance, wide-based gait, abnormal gait, cerebral palsy
57	48	*TP53*	p.Arg158His	P	U	autosomal dominant Li-Fraumeni Syndrome [MIM: 151623]	cerebellar ependymoma, cancer susceptibilitys, Li-Fraumeni syndrome
58	44	*SDHD*	p.Pro81Leu	P	U	autosomal dominant hereditary paraganglioma type 1 [MIM: 168000]	paraganglioma, papillary thyroid cancer, bowel incontinence, fatigue, tremors, fibroids, Von Hipple-Lindau syndrome, Multiple endocrine neoplasia type 2, Cowden syndrome, Li Fraumeni syndrome, cancer susceptibility
59	58	*SDHB*	p.Arg90*	P	U	autosomal dominant paragangliomas [MIM: 115310]	paraganglioma, Von Hipple-Lindau syndrome, Multiple endocrine neoplasia type 2, Cowden syndrome, Li Fraumeni syndrome, cancer susceptibility
60	3	*PTPN11*	p.Asn308Asp	P	U	autosomal dominant Noonan Syndrome 1 [MIM: 163950]	developmental delay, colobomas, supravalvular pulmonic stenosis, supravalvular aortic stenosis, short stature, CHARGE, growth hormone insensitivity ,nystagmus
61	8	*KRT16*	p.Gln122Arg	LP	U	autosomal dominant pachyonychia congenita [MIM: 167200]	heart defect, bicuspid aortic valve, aortic dilation, dilated aorta, hyperhidrosis, nail dystrophy, dental anomalies, Odonto-onycho-dermal dysplasia, dyskeratosis congenita
62	0	*EFTUD2*	Splice Defect	LP	U	autosomal dominant mandibulofacial dysostosis, Guion-Almeida type [MIM: 610536]	congenital anomalies, dysmorphic features, microcephaly, plagiocephaly, microretrognathia, hemivertebra, limb anomalies, esophageal atresia, inguinal hernia, respiratory failure, choanal atresia, cerebral atrophy, developmental delay, cryptorchidism, malar hypoplasia, Vater syndrome, Nager syndrome, Treacher Collins syndrome, Renpenning syndrome, Charge syndrome
63	49	*NOTCH3*	p.Arg1231Cys	P	U	autosomal dominant cerebral arteriopathy with subcortical infarcts; leukoencephalopathy [MIM: 125310]	ataxia, white matter changes, leukodystrophy, neuropathy, dementia, cognitive decline, vision loss
64	0	*NR5A1*	p.Tyr404Asp	P	U	46XY sex reversal 3 [MIM: 612965]; Adrenocortical insufficiency;	disorder of sexual development, XY female

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						Premature ovarian failure 7 [MIM: 612964]; Spermatogenic failure 8 [MIM: 613957]	
65	68	*FLCN*	p.His429Thrfs*39	P	U	autosomal dominant Birt-Hogg-Dube syndrome [MIM: 135150]; autosomal dominant primary spontaneous pneumothorax [MIM: 173600]	cancer susceptibility, Li Fraumeni, Lynch, Familial adenomatous polyposis, Cowden syndrome, bullous emphysema, lung hamartoma
66	55	*SPAST*	p.Arg562Gln	P	U	autosomal dominant spastic paraplegia 4 [MIM: 182601]	spasticity, Spastic paraparesis
67	8	*FGF23*	p.Gly87Asp	LP	U	autosomal dominant hyperphosphatemic familial tumoral calcinosis [MIM: 211900]	developmental delay, seizures, esotropia, amblyopia, anisometropia, vitreous hemorrhages, liver failure, cholestasis, Calcinosis, hypertrophy, obsessive compulsive disorder, Attention deficit hyperactivity disorder
68	13	*PCDH19*	p.Ala153Ile	LP	U	X-linked female-restricted early infantile epileptic encephalopathy type 9 (EIEE9) or Juberg-Hellman Syndrome [MIM: 300088]	epilepsy, seizures, learning disability, growth delay, bone age
69	26	*GATA2*	p.Tyr376Profs*9	P	U	autosomal dominant Emberger syndrome [MIM: 614038]	neutropenia, hearing loss, deafness, papillary thyroid cancer, cancer susceptibility
70	49	*CACNA1A*	p.Asp302Asn	LP	U	autosomal dominant spinocerebellar ataxia-6 [MIM:183086]; episodic ataxia type 2 [MIM:108500]; familial hemiplegic migraine-1 with progressive cerebellar ataxia [MIM:141500]	ataxia, nystagmus, diabetes
>2 LP/P reported							
71	29	*AR*	p.Pro392Ser	P	U	X-linked recessive partial Androgen insensitivity syndrome [MIM: 312300]; X-linked recessive hypospadias [MIM: 300633]	neuropathy, Charcot-Marie-Tooth, gait disturbance
71	29	*GDAP1*	p.Met116Thr	LP	U	autosomal recessive Charcot-Marie-Tooth disease [MIM: 607831, 607706, 608340,; 21440]	neuropathy, Charcot-Marie-Tooth, gait disturbance
71	29	*GDAP1*	p.Asp21Alafs*23	P	U	autosomal recessive Charcot-Marie-Tooth disease [MIM: 607831, 607706, 608340,; 21440]	neuropathy, Charcot-Marie-Tooth, gait disturbance
Trio-CES							

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De novo							
72	0	*TCF4*	Splice defect	LP	De novo	Pitt-Hopkins Syndrome [MIM: 610954]	developmental delay, hypertonia, elevated lactate, hypotonia, cerebral palsy, constipation, gastrointestinal motility, hirschsprung, arginase deficiency, angelman syndrome, fragile X
73	24	*COL6A2*	p.Gly699Asp	LP	De novo	Bethlem myopathy [MIM: 158810]; Myosclerosis, congenital [MIM: 255600]; Ullrich congenital muscular dystrophy [MIM: 254090]	muscular weakness, muscular atrophy, muscular, hypertrophic, spinal muscular atrophy, Charcot-Marie-Tooth, neuropathy, toe walking, gower's sign
74	8	*ZEB2*	p.Asp978Tyr	LP	De novo	Mowat-Wilson syndrome [MIM: 235730]	epilepsy, developmental delay, hypertonia, Lennox Gastaut syndrome, early puberty, spasticity, Nephrolithiasis, cerebellar hypometabolism, brain atrophy
75	0	*KCNT1*	p.Arg474His	P	De novo	malignant migrating partial seizures of infancy (MMPSI)	epilepsy, seizures, regression of milestone, developmental delay, sulfite oxidase deficiency, creatine disorders, Dravet syndrome, pyridoxine responsive, pyridoxine dependent, folinic acid response
76	4	*RAD21*	p.Leu603Pro	LP	De novo	autosomal dominant Cornelia de Lange syndrome 4 [MIM: 614701]	microcephaly, language delay, speech delay, dysmorphic features, williams syndrome, kabuki syndrome, tooth enamel, large ears, long palpebral fissure, high arched eyebrows, high arched palate, long eyelashes, clinodactyly
77	1	*ACVR1*	p.Arg258Gly	LP	De novo	fibrodysplasia ossificans progressive (FOP) [MIM: 135100]	Craniofacial abnormalities, deafness, dysmorphic features, macrocephaly, unilateral sensorineural hearing loss, motor delay, congenital anomalies, 4-limb digit hypoplasia, disproportionate limbs, joint restrictions, ventriculomegaly, brain stem deformity, skeletal abnormalities, ectodermal dysplasia, hydrocephalus, subcutaneous masses, storage disorder, mucopolysaccharidosis, metabolic disorder, lysosomal disorder, Fibrodysplasia ossificans progressiva
78	0	*SCN2A*	p.Ser987Ile	LP	De novo	early infantile epileptic encephalopathy type 11 [MIM: 613721] or benign familial infantile seizures type 3 [MIM: 607745]	seizures, vomiting, developmental delay, otitis media

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79	0	*SCN8A*	p.Arg850Gln	LP	De novo	Cognitive impairment with or without cerebellar ataxia [MIM: 614306]; Epileptic encephalopathy, early infantile, 13 [MIM: 614558]	deafness, hearing impairment, developmental delay, seizures, infantile spasms
80	1	*KRAS*	p.Asp153Val	P	De novo	autosomal dominant Noonan Syndrome type 3 [MIM: 609942]	developmental delay, dysmorphic features, costello syndrome, noonan syndrome, pulmonary stenosis, astigmatism, nystagmus, undescended testicle, hypertelorism, diastasis, hypotonia
81	4	*TUBB4A*	p.Val255Ile	LP	De novo	Dystonia 4, torsion, autosomal dominant [MIM: 128101]; Leukodystrophy, hypomyelinating, 6 [MIM: 612438]	developmental delay, microcephaly, truncal hypotonia, cerebellar hypoplasia, limb hypertonia, hyperreflexia, depressed nasal bridge, cerebellar atrophy, bilateral clonus of the feet, brain malformation
82	0	*MAP2K2*	p.Lys61Glu	LP	De novo	autosomal dominant Cardiofaciocutaneous Syndrome (CFCS) [MIM: 115150]	Noonan, Hydrocephalus, seizures, Pulmonary artery stenosis, dysmorphic features, Heart murmur, developmental delay, ventriculomegaly
83	2	*DYRK1A*	p.Tyr104 *	LP	De novo	autosomal dominant mental retardation type 7 [MIM:614104]	developmental delay, dysmorphic features, iron deficiency, metabolic disorder, microcephaly, poor weight gain, short stature, strabismus
84	6	*PIK3CA*	p.Gly914Arg	LP	De novo	megalencephaly-capillary malformation-polymicrogyria syndrome (MCAP) [MIM: 602501]	Bilateral cryptorchidism, constipation, developmental delay, dolichocephaly, duplicated/bifid collecting system, dysrmophi*, hydrocephalus, hypotonia, inguinal hernia, laryngomalacia, leg length, macrocephaly, postaxial polydactyly, Simpson-Golabi-Behmel syndrome, syndactyly
85	13	*FOXP1*	p.Val423His fs*37	LP	De novo	intellectual disability with language impairment; autistic features [MIM: 613670]	Abnormal gait, ADHD, autism, dysmorphic features, foot drag, hypophonia, macrocephaly, mitochondrial, muscular dystrophy, neuromuscular disorder, obsessive behavior
86	4	*ADAR*	p.Gly1007Arg	LP	De novo	autsomal dominant Aicardi-Goutieres syndrome type 6 [MIM: 615010]; dyschromatosis symmetrica hereditaria [MIM: 127400]	paraparesis, weakness, abnormal reflex, muscle tone, coordination, spasticity, diplegia, leukodystrophy, Babinski's sign, mitochondrial
87	0	*KMT2A(MLL)*	Splice defect	LP	De novo	Wiedemann-Steiner syndrome [MIM: 605130]	developmental delay, dysmorphic features, growth retardation, hypotonia, micrognathia, microphthalmia, optic nerve coloboma, orbital

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							cysts, pectus excavatum, poor growth, retinal detachment, syndactyly, turned-out hands, wide fontanelle
88	7	*CRX*	p.Glu42Lys	LP	De novo	Cone-rod retinal dystrophy-2 [MIM: 120970]; Leber congenital amaurosis 7 [MIM: 613829]	Leber's congenital amaurosis, light perception, macular atrophy, nystagmus, retinal atrophy, visual acuity.
89	14	*HUWE1*	p.Ala1338Val	LP	De novo	Turner type intellectual disability syndrome [MIM: 300706]	developmental delay, hip dysplasia, hypermobility, joint laxity, seizures, epilepsy, dysmorphic
90	3	*SCN2A*	p.Arg853Gln	LP	De novo	Epileptic encephalopathy, early infantile, 11 [MIM: 613721]; seizures, benign familial infantile, 3 [MIM: 607745]	developmental delay, spasms, seizures, epilepsy, renal lithiasis, kidney stone, involuntary movements, rotary nystagmus, vomit, gastroesophageal reflux, feeding intolerance.
91	6	*SCN2A*	p.Glu1211Lys	LP	De novo	Epileptic encephalopathy, early infantile, 11 [MIM: 613721]; seizures, benign familial infantile, 3 [MIM: 607745]	developmental delay, epilepsy, seizures, spasms, autism, Microcephaly, wide palpebral fissures, hypertonia, mitochondrial, complex IV, cytochrome c oxidase deficiency , Rett syndrome, Lennox Gastaut
92	3	*HDAC8*	Splice defect	LP	De novo	X-linked dominant Cornelia de Lange Syndrome [MIM: 30882]	microcephaly, brachycephaly, developmental delay, Cornelia De Lange, asymmetric facies, short stature, low weight, brachydactyly, clinodactyly
93	1	*NSD1*	p.Gln784*	LP	De novo	autosomal dominant Beckwith-Wiedemann syndrome [MIM: 130650]; autosomal dominant Sotos syndrome 1 [MIM: 117550]	brain malformation, hypoxic ischemic encephalopathy, craniofacial abnormalities, developmental delay, auditory neuropathy, dysmorphic features, hypotonia, cortical vision ,micrognanthia, small Patent ductus arteriosus
94	23	*PTEN*	p.Ser287*	LP	De novo	autosomal dominant PTEN hamartoma tumor syndrome including Bannayan-Riley-Ruvalcaba syndrome [MIM: 153480]; Cowden syndrome 1 [MIM: 158350]; macrocephaly/autism syndrome [MIM: 605309]	PTEN hamartoma tumor syndrome, macrocephaly, tinnitus, hearing loss, early permanent dentition, precocious puberty, cutis scarring, menorrhagia, Cowden Syndrome, collagen syndrome, kyphosis, scoliosis, balance, migraines
95	3	*GARS*	p.Glu333Val	LP	De novo	autosomal dominant Charcot-Marie-Tooth disease type 2 [MIM: 601472]; distal hereditary motor neuronopathy type V [MIM: 600794]	weakness, respiratory, myopathy, neuropathy, gait, muscular dystrophy

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96	0	*KAT6B*	p.Gln1321Argfs*20	LP	De novo	autosomal dominant Say-Barber-Biesecker-Young-Simpson Syndrome (SBBYSS) [MIM: 603736]	CHARGE syndrome, multiple congenital anomalies, nasolacrimal duct obstruction, ear anomaly, heart murmur, hypotonia, hydronephrosis, microcephaly, Simian crease, Myasthenia gravis
97	21	*CHD8*	p.Arg773*	LP	De novo	autism type 18 [MIM: 615032]	autism, scoliosis, thyroid, learning disabilities, dysmorphic features, tall stature, epicanthal folds, palpebral fissures, thin nasal bridge, high-arched palate, narrow facies, long thin fingers, toes
98	2	*DYRK1A*	p.Lys188Ile	LP	De novo	intellectual disability type 7 [MIM: 614104]	developmental delay, microcephaly, dysmorphic features, hypertonia, micrognathia, spasticity, clinodactyly, tapering fingers
99	12	*ITPR1*	p.Ser277Ile	LP	De novo	Spinocerebellar ataxia 15 [MIM: 606658]; Spinocerebellar ataxia 29, congenital nonprogressive [MIM: 117360]	brain malformation, cerebellar hypoplasia, developmental delay, ataxia, dysmetria, vermian hypoplasia, strabismus, constipation
100	36	*PSEN1*	p.Leu381Val	P	De novo	autosomal dominant early onset dementia with or without spastic paraparesis [MIM: 607822]	spasticity, cognitive decline, increased tone, hypertonia, increased reflexes, Hyperreflexia, vision loss
101	6	*SHOC2*	p.Ser2Gly	LP	De novo	Noonan syndrome-like disorder with loose anagen hair [MIM: 607721]	Short stature, macrocephaly, hypotonia, motor delay, speech delay, eczema, bulging fontanel, heart defect, dysmorphic features, bathrocephaly, skeletal dysplasia, hypochondroplasia
102	1	*ZEB2*	p.Leu727Tyrfs*7	LP	De novo	Mowat-Wilson syndrome [MIM: 235730]	developmental delay, hypotonia, heart disease, growth delay, Mowat-Wilson syndrome, constipation, tachycardia, hypospadias, dysmorphic features, Kleefstra syndrome, cortical blindness, visual impairment, postural abnormalities
103	2	*NR2F1*	p.Cys128Arg	LP	De novo	Bosch-Boonstra-Schaaf optic atrophy syndrome [MIM: 615722]	autism, developmental delay, spasms, seizures, failure to thrive, sensorineural hearing loss, microtia
104	14	*KCNMA1*	p.Thr352Ala	LP	De novo	generalized epilepsy; paroxysmal dyskinesia [MIM: 609446]	developmental delay, seizures, hypotonia, scoliosis, cerebral palsy, neuromuscular
105	2	*SYNGAP1*	p.Arg299Profs*48	P	De novo	autosomal dominant intellectual disability type 5 [MIM: 612621]	autism, developmental delay, milk intolerance, GERD
106	17	*GRIN2B*	p.Arg682Cys	P	De novo	autosomal dominant intellectual disability type 6 [MIM: 613970]	scoliosis, hypotonia, developmental delay, learning disability, language delay, attention

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							deficit disorder
107	11	*TUBB2A*	p.Gln291Pro	LP	De novo	Cortical dysplasia, complex, with other brain malformations 5 [MIM: 615763]	developmental delay, short stature, seizures, ureteropelvic junction obstruction, constipation, hydronephrosis, clinodactyly, growth hormone deficiency, Russell Silver syndrome
108	5	*KCNT1*	p.Arg464His	P	De novo	autosomal dominant early infantile epileptic encephalopathy [MIM: 61459]; autosomal dominant nocturnal frontal lobe epilepsy 5 [MIM: 615005]	developmental delay, cortical blindness, seizures, cerebral palsy
109	4	*MPZ*	p.Gly167Arg	P	De novo	Charcot-Marie-Tooth disease, dominant intermediate D [MIM: 607791]; Charcot-Marie-Tooth disease, type 1B [MIM: 118200]; Charcot-Marie-Tooth disease, type 2I [MIM: 607677]; Charcot-Marie-Tooth disease, type 2J [MIM: 607736]; Dejerine-Sottas disease [MIM: 145900]; Neuropathy, congenital hypomyelinating [MIM: 605253]; Roussy-Levy syndrome [MIM: 180800]	charcot marie tooth, neuropathy
110	13	*HSPD1*	p.Ala536Val	LP	De novo	autosomal dominant spastic paraplegia 13 [MIM: 605280]; autosomal recessive hypomyelinating leukodystrophy 4 [MIM: 612233]	ataxia, white matter disease, nystagmus, hypomyelination, Pelizaeus Merzbacher disease, mitochondrial encephalopathy, myopia, astigmatism
111	0	*KCNQ2*	p.Gly281Trp	P	De novo	autosomal dominant early infantile epileptic encephalopathy-7 [MIM: 613720]	seizures, encephalopathy, dysmorphic features, metabolic disorders, thin corpus callosum, pectus excavatum, dermal melanosis, carnitine deficiency, hypotonia, congenital disorder of glycosylation, peroxisomal disorder, Zellweger, lysosomal storage disorder
112	17	*CAMTA1*	p.Tyr1077Cys	LP	De novo	autosomal dominant nonprogressive cerebellar ataxia with intellectual disability [MIM: 614756]	autism, developmental delay, catatonia, psychosis, attention deficit disorder
113	1	*TUBB2A*	p.Ile345Phe	LP	De novo	Cortical dysplasia, complex, with other brain malformations 5 [MIM: 615763]	developmental delay, epilepsy, seizures, infantile spasms, perisylvian polymicrogyria, microcephaly, plagiocephaly

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114	13	*ATP1A3*	p.Gly325Asp	LP	De novo	autosomal dominant dystonia 12 [MIM: 128235]; autosomal dominant alternating hemiplegia of childhood 2 [MIM: 614820]	developmental delay, ataxia, seizures, spasticity, cerebellar atrophy, strabismus, exotropia, legally blind, dysmorphic features, ankyloglossia
115	5	*CHD8*	p.Arg582*	LP	De novo	autosomal dominant susceptibility to autism type 18 [MIM: 615032]	autism, developmental delay, muscular dystrophy, diabetes , mitochondrial
116	1	*KMT2A*	p.Lys1218Glufs*4	P	De novo	autosomal dominant Wiedemann-Steiner syndrome [MIM: 605130]	developmental delay, torticollis, hypotonia, dysmorphic features, gastroesophageal reflux, gastrostomy, hypertrichosis, Hirsutism, mitochondria
117	14	*SRCAP*	p.Arg2435*	P	De novo	autosomal dominant Floating-Harbor syndrome [MIM: 136140]	develomental delay, speech delay, short stature, microcephaly, dysmorphic features, ptosis, brachydactyly, Coffin-Siris syndrome, Kabuki
118	6	*PTPN11*	p.Asn308Asp	P	De novo	autosomal dominant Noonan syndrome 1 [MIM: 163950]	developmental delay, seizures, dysmorphic features, short stature, ptosis, pectus excavatum, cardiac defect, atrial enlargement, subarachnoid hemorrhage, myopia, constipation, RASopathy, Noonan
119	2	*SMARCA2*	p.His1161Arg	LP	De novo	autosomal dominant Nicolaides-Baraitser syndrome [MIM: 601358]	developmental delay, seizures, dysmorphic features, microcephaly, undescended testicles, white matter changes, leukodystrophy
120	0	*KMT2D*	p.Gln3759*	P	De novo	autosomal dominant Kabuki syndrome [MIM: 147920]	heart defect, cardiac defect, coarctation of the aorta, supraventricular tachycardia, duplex kidneys, gastroesophageal reflux, otitis media, hypotonia, developmental delay, Noonan, Kabuki
121	3	*TCF4*	p.Gly656Argfs*55	P	De novo	autosomal dominant Pitt-Hopkins syndrome [MIM: 610954]	developmental delay, hypotonia, peripheral hypertonia, leukodystrophy, white matter changes, optic atrophy, esotropia, monocular, myopia, astigmatism
122	4	*SMARCA2*	p.Asp534Tyr	LP	De novo	autosomal dominant Nicolaides-Baraitser Syndrome [MIM: 601358]	developmental delay, micrognathia, nystagmus, dysmorphic features, microcephaly, Hallermann–Streiff, Cornelia de Lange Syndrome
123	3	*SATB2*	p.Thr390Ile	LP	De novo	autosomal dominant Glass Syndrome [MIM: 612313]	developmental delay, dysmorphic features, microcephaly, supernumerary teeth, pyruvate dehydrogenase deficiency, myopathic face, hypotonia, neuromuscular, inguinal hernia, undescended testes, Williams syndrome, Noonan syndrome, Angelman syndrome

Patient Index	Age	Gene Name	Protein Change	Variant Class	Inherited From	Disease Name	Clinical Indication*
124	9	*LMNA*	Splice defect	P	De novo	autosomal dominant limb-girdle muscular dystrophy [MIM: 159001], autosomal dominant congenital muscular dystrophy [MIM: 613205]; autosomal dominant Emery-Dreifuss muscular dystrophy 2 [MIM: 181350]	ataxia, muscular dystrophy, myopathy
125	16	*CTNNB1*	p.Leu424Arg	LP	De novo	autosomal dominant intellectual disability 19 [MIM: 615075]	developmental delay, microcephaly, brachycephaly, dysmorphic features, cerebral palsy, scoliosis, gait abnormality
126	3	*CHD7*	p.His1734Serfs*3	P	De novo	autosomal dominant CHARGE syndrome[MIM: 214800]	developmental delay, bicuspid aortic valve, atrial septal aneurysm, patent foramen ovale, atrial septal defect, dysmorphic features, craniofacial, gastroesophageal reflux, laryngomalacia, hearing loss, deafness, astigmatism, constipation, Otopalatodigital syndrome, CHARGE syndrome, 3M syndrome
127	0	*CASK*	Splice defect	P	De novo	X-linked dominant intellectual disability; microcephaly with pontine; cerebellar hypoplasia (MICPCH) [MIM: 300749]	developmental delay, nystagmus, hypotonia, pontocerebellar atrophy, pontocerebellar hypoplasia, Polymicrogyria, microcephaly, hearing loss, deafness, seizures, epilepsy
128	0	*KCNK9*	p.Gly236Arg	P	De novo	autosomal dominant Birk-Barel intellectual disability dysmorphism syndrome [MIM: 612292]	developmental delay, dysmorphic features, cleft palate, craniofacial, microcephaly, retrognathia, micrognathia, hypertelorism, hypotonia, hypoglycemia, hyperinsulinemia, intrauterine growth restriction, Stickler syndrome
129	12	*NSD1*	p.Glu1184*	LP	De novo	Sotos syndrome [MIM:117550]	seizures, epilepsy, developmental delay, dysmorphic features, craniofacial abnormalities , long narrow face, large forehead, malar hypoplasia, lowset posteriorly rotated ear, epicanthal folds bilaterally, high arched palate, kyphosis, scoliosis, broad fingers, toes, joint laxity, inverted nipples, mild pectus excavatum
130	8	*MLL*	p.Cys1448Arg	LP	De novo	autosomal dominant Wiedemann-Steiner Syndrome [MIM: 605130]	developmental delay, hypotonia, myopathy, ptosis, dysmorphic features, craniofacial abnormalities, hypertelorism, bulbous nose, clinodactyly, tapering fingers, downslanting palpebral fissures, wide nasal bridge,

Patient Index	Age	Gene Name	Protein Change	Variant Class	Inherited From	Disease Name	Clinical Indication*
							astigmatism, early tooth eruption, premature adult teeth
131	4	*TUBA1A*	p.Val118Met	LP	De novo	autosomal dominant lissencephaly 3 [MIM: 611603]	brain malformation, developmental delay, spasticity, hyperreflexia, wide based gait
132	1	*KMT2A*	p.Ser3446Phefs*29	P	De novo	autosomal dominant Wiedemann-Steiner syndrome [MIM: 605130]	developmental delay, short stature, ptosis, hypotonia
Homozygous							
133	2	*SURF1*	Splice Defect	LP	Both	Leigh syndrome, due to COX deficiency [MIM: 256000]	hypotonia, lactic acidosis, failure to thrive , neurological deterioration
134	0	*NDUFS8*	p.Lys115Glu	LP	Both	Leigh syndrome [MIM:256000]	respiratory failure, metabolic acidosis, metabolic disorder, lactic acidosis, mitochondrial disorder, pyruvate dehydrogenase complex deficiency, white matter necrosis, ventricular hypertrophy, hepatic steatosis, iliac artery thrombosis, Leigh's disease
135	15	*KCNJ13*	p.Thr153Ile	LP	Both	Leber congenital amaurosis [MIM: 614186]	Leber congenital amaurosis, cone-rod dystrophy, cone rod dystrophy, nystagmus, night blindness, photophobia, color disturbances, atrophic changes in macular, macular atrophy
136	6	*SLC35C1*	p.Thr291Ile	LP	Both	leukocyte adhesion deficiency II (LAD2) [MIM: 266265]	developmental delay, failure to thrive, feeding problem, feeding issue, cytochrome C oxidase, citrate synthase, complex IV, mitochondria, duplex collecting system, ectopic ureter, toe-walking, poor growth, brain atrophy
137	19	*ALDH18A1*	p.Arg765Gln	LP	Both	autosomal recessive cutis laxa, type IIIA (ARCL3A) [MIM: 219150]	developmental delay, delayed milestones, microcephaly, seizures, hypotonia, autism, self injurious, involuntary movements, cognitive deficit, sleep disturbance, metabolic disorders
138	0	*GLDC*	p.Pro581Arg	LP	Both	autosomal recessive non-ketotic hyperglycinemia [MIM: 605899]	micrognathia, hypotonia, prominent forehead, seizures, respiratory failure, dysmorphic features, failure to thrive
139	1	*USH2A*	p.Ser3276*	LP	Both	autosomal recessive Usher Syndrome type 2A [MIM: 276901]	Deafness, hearing loss
140	0	*ALDH7A1*	p.Glu427Gln	LP	Both	pyridoxine-dependent epilepsy [MIM: 266100]	seizures, developmental delay, hydrocephalus.
141	26	*TCAP*	p.Ser11*	LP	Both	autosomal recessive Limb-girdle muscular dystrophy type 2G [MIM: 601954]	muscular dystrophy, myopathy, muscle weakness

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142	9	*GJB2*	p.Val37Ile	LP	Both	Bart-Pumphrey syndrome [MIM: 149200]; Deafness, autosomal dominant 3A [MIM: 601544]; Deafness, autosomal recessive 1A [MIM: 220290]; Hystrix-like ichthyosis with deafness [MIM: 602540]; Keratitis-ichthyosis-deafness syndrome [MIM: 148210]; Keratoderma, palmoplantar, with deafness [MIM: 148350]; Vohwinkel syndrome [MIM: 124500]	jerks, hearing loss, seizures, dystonic head movements, enchondroma
143	0	*CRLF1*	p.Pro239Alafs*91	P	Both	autosomal recessive Crisponi syndrome (cold-induced sweating syndrome type 1) [MIM: 272430]	developmental delay, camptodactyly, feeding intolerance, hydronephrosis, Schwartz-Jampel syndrome, hypertonia, dysmorphic features, micrognathia, Crisponi syndrome
144	13	*ACOX1*	p.Arg59Pro	LP	Both	autosomal recessive adrenoleukodystrophy due to peroxisomal acyl-CoA oxidase deficiency [MIM: 264470]	developmental delay, degenerative brain, demyelination, dysmyelination, brain atrophy, corpus callosum, brainstem, cognitive dysfunction, ataxia, pyramidal tract signs, color vision, optic atrophy, astigmatism, quadriparesis, spasticity, bowel dysfunction, bladder dysfunction
145	16	*SH3TC2*	p.Arg954*	P	Both	autosomal recessive Charcot-Marie-Tooth Disease (CMT) type 4C [MIM: 601596]	spasms, contractures, Achilles tendon release, cerebral palsy, scoliosis, muscle weakness, hyperflexible, sensory deficits, areflexia, neuropathy, demyelination, Charcot Marie Tooth, fasciculations
146	6	*PRF1*	p.Gln446Pro	LP	Both	autosomal recessive familial hemophagocytic lymphohistiocytosis type 2 [MIM: 603553]	immunodeficiency, hemophagocytic lymphohistiocytosis, fever, splenomegaly, decreased NK cell activity, elevated IL-2 receptor, cytopenia
147	12	*FA2H*	p.Pro173Ser	LP	Both	autosomal recessive spastic paraplegia type 35 (SPG35) [MIM: 612319]	mitochondrial, gait disturbance, spasticity, hyperreflexia, muscle weakness, metabolic disorders, leukopathy
148	22	*RPL44*	p.Leu156Arg	LP	Both	autosomal recessive combined oxidative phosphorylation deficiency type 16 [MIM: 615395]	cardiomyopathy, myopathy, kidney disease, mitochondrial, arrhythmia, muscle weakness
149	0	*RRM2B*	p.Gly212_Leu213insSer	LP	Both	autosomal recessive mitochondrial DNA depletion syndrome types 8A; 8B [MIM: 612075]	mitochondrial disorder, poor feeding, hypotonia, progressive weakness, respiratory failure, developmental delay, retinopathy, elevated lactic acid, increased Krebs cycle

Patient Index	Age	Gene Name	Protein Change	Variant Class	Inherited From	Disease Name	Clinical Indication*
150	4	*MTFMT*	p.Pro373Glnfs*19	LP	Both	autosomal recessive combined oxidative phosphorylation deficiency type 15 [MIM: 611766]	developmental delay, seizures, stroke, moyamoya, failure to thrive, heart defect, pulmonic stenosis, carotid stenosis, end stage renal disease, anemia, hypertension, bone mineral disease, vesicoureteral reflux, neurovascular abnormalities, dysmorphic features, Peritonitis, Alagille syndrome
151	0	*TRMU*	p.Leu253Pro	LP	Both	autosomal recessive transient infantile liver failure [MIM: 613070]	liver failure, metabolic disorders, hyperbilirubinemia, thrombocytopenia, anemia, direct hyperbili, lactic acidosis, transaminitis, mitochondrial disorder
152	4	*PLA2G6*	p.Gly373Arg	P	Both	autosomal recessive infantile neuroaxonal dystrophy 1 (neurodegeneration with brain iron accumulation types 2A; 2B) [MIM: 256600] [MIM: 610217]	autism, developmental delay, developmental regression, congenital anomalies, microcephaly, cerebral palsy, pontocerebellar hypoplasia, encephalopathy, spasticity, hypotonia, ataxia
Hemizygous							
153	5	*ATRX*	p.Pro190Ala	LP	M	Alpha-thalassemia myelodysplasia syndrome, somatic [MIM: 300448]; Alpha-thalassemia/mental retardation syndrome [MIM: 301040]; Mental retardation-hypotonic facies syndrome, X-linked [MIM: 309580]	hypotonia, developmental delay, craniosynostosis, microcephaly, scaphocephaly, trigonocephaly, seizures, epilepsy, dysmorphic features, camptodactyly, amblyopia, nystagmus, ptosis, entropion, myopia, astigmatism, optic nerve hypoplas*, undescended testicle*
154	41	*RPGR*	p.Glu1060ArgfsX18	LP	M	X-linked cone-rod dystrophy [MIM: 304020]	cone dystrophy, stargardt
155	2	*KDM6A*	p.Arg1279*	LP	M (mosaic)	Kabuki Syndrome [MIM: 300867]	developmental delay, failure to thrive, abdominal pain, seizures, breath holding spell, facial dysmorphic features, prominent eyes, long eyelashes, short nose, anteverted nares, increased lipid on muscle biopsy, hypertonia, metabolic disorder, autoimmune disorder, familial mediterranean fever, Rubinstein Taybi syndrome, pilomatricoma formation, erythromelalgia
156	3	*MED12*	p.Thr617Ala	LP	M	X-Linked Intellectual Disability Syndromes: Lujan-Fryns Syndrome [MIM:309520]; Opitz-Kaveggia Syndrome [MIM: 305450]	autism, craniofacial, dysmorphic features, epicanthal folds, language, mid face hypoplasia

Patient Index	Age	Gene Name	Protein Change	Variant Class	Inherited From	Disease Name	Clinical Indication*
157	18	*IL2RG*	p.Val152Ala	P	M	X-linked recessive severe combined immunodeficiency [MIM: 300400]	SCID, immunodeficiency, granulomas, skin rash, epidermodysplasia verruciformis, warts, pyoderma gangrenosum.
158	0	*CLCNKB*	p.Leu633*	LP	F*	autosomal recessive Bartter Syndrome type 3 [MIM: 607364]	Bartter, chloride channel, Gitelman, hypochloremic, hypokalemic, hyponatremic, lethargy
159	1	*ATRX*	p.Arg2131Gln	P	M	X-linked recessive intellectual disability with hypotonic facies syndrome [MIM: 309580]	developmental delay, failure to thrive, hypotonia, cerebral palsy, dysmorphic features, Secundum Atrial Septal Defects, heart defect
160	2	*BRWD3*	p.Leu1419Val	LP	M	X-linked intellectual disability type 93 [MIM: 300659]	autism, developmental delay, macrocephaly, hypotonia, dysmorphism
161	22	*G6PD*	p.Ser188Phe	P	M	glucose-6-phosphate deficiency in males [MIM: 305900]	rod-cone dystrophy , peripheral vision loss, central vision loss, retinitis pigmentosa, Glucose 6-Phosphatase deficiency
Compound Heterozygous							
162	0	*RAPSN*	p.Gln175Arg	LP	F	autosomal recessive congenital myasthenic syndrome associated with facial dysmorphism; acetylcholine receptor deficiency [MIM: 608931]; autosomal recessive fetal akinesia deformation sequence [MIM: 208150]	myopathy, hypotonia, contractures, oropharyngeal dysphagia, intrauterine growth restriction dysmorphic features, distal arthrogryposis, areflexia, respiratory distress, EMARDD
162	0	*RAPSN*	p.Thr277Ala	LP	M	autosomal recessive congenital myasthenic syndrome associated with facial dysmorphism; acetylcholine receptor deficiency [MIM: 608931]; autosomal recessive fetal akinesia deformation sequence [MIM: 208150]	myopathy, hypotonia, contractures, oropharyngeal dysphagia, intrauterine growth restriction dysmorphic features, distal arthrogryposis, areflexia, respiratory distress, EMARDD
163	1	*SLC12A1*	p.Tyr245*	P	M	autosomal recessive Bartter syndrome, antenatal, type 1 [MIM: 601678]	Bartter, hypercalcemia, hyperparathyroidism, hyponatremia, hypokalemia, Nephrogenic diabetes insipidus, medullary nephrocalcinosis, polyuria, short stature, growth failure
163	1	*SLC12A1*	p.Ala508Thr	P	F	autosomal recessive Bartter syndrome, antenatal, type 1 [MIM: 601678]	Bartter, hypercalcemia, hyperparathyroidism, hyponatremia, hypokalemia, Nephrogenic diabetes insipidus, medullary nephrocalcinosis, polyuria, short stature, growth failure
164	15	*B3GALNT2*	p.Glu480_Trp485	LP	F	autosomal recessive congenital	muscular dystrophy, autism, developmental

Patient Index	Age	Gene Name	Protein Change	Variant Class	Inherited From	Disease Name	Clinical Indication*
			dup			muscular dystrophy-dystroglycanopathy with brain; eye anomalies type A, 11 [MIM: 615181]	delay, hypotonia, polymicrogyria, cerebellar cortical cysts
164	15	*B3GALNT2*	p.Asp327Asn	LP	M	autosomal recessive congenital muscular dystrophy-dystroglycanopathy with brain; eye anomalies type A, 11 [MIM: 615181]	muscular dystrophy, autism, developmental delay, hypotonia, polymicrogyria, cerebellar cortical cysts
165	3	*TBC1D24*	p.Trp406Cys	LP	F	familial or infantile myoclonic epilepsy [MIM: 613577]	developmental delay, epilepsy, seizures, hypoplastic corpus callosum, lysosomal storage disorder, neuronal ceroid lipofuscinosis disorder, paroxysmal disorder, Angelman, Rett syndrome, spasticity, zellweger, adrenoleukodystrophy, Krabbe's disease, Niemann Pick Type A, Glutaric Aciduria Type 1, Tay Sachs
165	3	*TBC1D24*	p.Cys424Arg	LP	M	familial or infantile myoclonic epilepsy [MIM: 613577]	developmental delay, epilepsy, seizures, hypoplastic corpus callosum, lysosomal storage disorder, neuronal ceroid lipofuscinosis disorder, paroxysmal disorder, Angelman, Rett syndrome, spasticity, zellweger, adrenoleukodystrophy, Krabbe's disease, Niemann Pick Type A, Glutaric Aciduria Type 1, Tay Sachs
166	8	*CLN8*	p.Leu188Valfs	P	F	neuronal ceroid lipofuscinosis (NCL) [MIM:600143]	retinitis pigmentosa, cone rod dystrophy, vision loss, neuronal ceroid lipofuscinosis, seizures, hyperactivity, attention deficit, inattention, behavioral difficulties, disruptive behavior, ADHD, refsum disease, ciliopathy
166	8	*CLN8*	p.Ala71Val	LP	M	neuronal ceroid lipofuscinosis (NCL) [MIM:600143]	retinitis pigmentosa, cone rod dystrophy, vision loss, neuronal ceroid lipofuscinosis, seizures, hyperactivity, attention deficit, inattention, behavioral difficulties, disruptive behavior, ADHD, refsum disease, ciliopathy
167	31	*CNGB3*	p.Arg403Gln	P	F	autosomal recessive juvenile onset macular dystrophy (Stargardt Disease) [MIM: 248200]	retinitis pigmentosa, peripheral vision, panretinal abnormalities, bull's eye, maculopathy, peripapillary sparing
167	31	*CNGB3*	p.Tyr398Cys	LP	M	autosomal recessive juvenile onset macular dystrophy (Stargardt Disease) [MIM: 248200]	retinitis pigmentosa, peripheral vision, panretinal abnormalities, bull's eye, maculopathy, peripapillary sparing
168	3	*POLR3B*	p.Val523Glu	LP	F	autosomal recessive	deafness, hearing loss, neonatal teeth, teeth

Patient Index	Age	Gene Name	Protein Change	Variant Class	Inherited From	Disease Name	Clinical Indication*
						hypomyelinating leukodystrophy type 8 [MIM:614381]	eruption , dental eruption , weight gain, short stature, ectodermal dysplasia, Pendred syndrome, Mondini malformation, ataxia
168	3	*POLR3B*	p.Thr663Ile	LP	M	autosomal recessive hypomyelinating leukodystrophy type 8 [MIM:614381]	deafness, hearing loss, neonatal teeth, teeth eruption , dental eruption , weight gain, short stature, ectodermal dysplasia, Pendred syndrome, Mondini malformation, ataxia
169	25	*CERKL*	p.Arg257*	P	F	autosomal recessive retinitis pigmentosa type 26 (RP26) [MIM: 608380]	night blindness, central vision, bull's eye, peripheral vision, color disturbance, light adaptation, dark adaptation, retinitis pigmentosa
169	25	*CERKL*	p.Asp225Val	LP	M	autosomal recessive retinitis pigmentosa type 26 (RP26) [MIM: 608380]	night blindness, central vision, bull's eye, peripheral vision, color disturbance, light adaptation, dark adaptation, retinitis pigmentosa
170	2	*GOSR2*	p.Gly144Trp	P	F	autosomal recessive progressive myoclonic epilepsy, type 6 [MIM: 614018]	hypotonia, muscular dystrophy, chronic transaminitis, cyanosis , developmental delay, Scoliosis, lack of white matter , thin corpus callosum, rotatory nystagmus, fine hair, cartilage tear syndrome, metaphysic, earlobes, right undescended testicle, Walker-Warburg syndrome
170	2	*GOSR2*	Splice defect	LP	M	autosomal recessive progressive myoclonic epilepsy, type 6 [MIM: 614018]	hypotonia, muscular dystrophy, chronic transaminitis, cyanosis , developmental delay, Scoliosis, lack of white matter , thin corpus callosum, rotatory nystagmus, fine hair, cartilage tear syndrome, metaphysic, earlobes, right undescended testicle, Walker-Warburg syndrome
171	3	*GLB1*	p.Thr82Met	P	F	GM1-Gangliosidosis type 1 [MIM:230500]	developmental delay, hypotonia, hypotonia, speak OR speech, bilateral hip dysplasia, waddling gait, esotropia, snore, myopathy, Obstructive Sleep Apnea, cerebellar volume loss, small cerebellum, cerebellar atrophy, cerebellar hypoplasia, white matter, abnormal brain MRI, mitochondrial, very long chain fatty acids, glycosylation disorder
171	3	*GLB1*	p.Gly123Arg	P	M	GM1-Gangliosidosis type 1 [MIM:230500]	developmental delay, hypotonia, bilateral hip dysplasia, waddling gait, esotropia, myopathy, Obstructive Sleep Apnea, cerebellar atrophy, cerebellar hypoplasia, white matter, abnormal

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							brain MRI, mitochondrial, very long chain fatty acids, glycosylation disorder
172	1	*IMGHMBP2*	p.Trp31*	LP	M	autosomal recessive distal spinomuscular atrophy type 1 (SMARD1) [MIM:604320]	spinal muscular atrophy with respiratory distress
172	1	*IMGHMBP2*	p.Lys220Asn	LP	F	autosomal recessive distal spinomuscular atrophy type 1 (SMARD1) [MIM:604320]	spinal muscular atrophy with respiratory distress
173	6	*DHTKD1*	p.Arg715Cys	LP	F	autosomal recessive 2-aminoadipic 2-oxoadipic aciduria [MIM:204750]	2-ketoadipic, alpha-aminoadipic aciduria, dizziness, Esotropia, failure to thrive, headache, head-tilting, lysine metabolism, microcephaly, migraine, nausea, pansinusitis, patent ductus arteriosus, Still's murmur, tryptophan metabolism
173	6	*DHTKD1*	p.Gly729Arg	LP	M	autosomal recessive 2-aminoadipic 2-oxoadipic aciduria [MIM:204750]	2-ketoadipic, alpha-aminoadipic aciduria, dizziness, Esotropia, failure to thrive, headache, head-tilting, lysine metabolism, microcephaly, migraine, nausea, pansinusitis, patent ductus arteriosus, Still's murmur, tryptophan metabolism
174	60	*MEFV*	p.Ala744Ser	LP	M	autosomal recessive familial Mediterranean fever [MIM: 249100]	Stroke, neurocognitive, neurodegenerative, mitochondrial, encephalopathy, aphasia, weakness, muscle jerks, hallucinations, tremors.
174	60	*MEFV*	p.Lys695Arg	LP	F	autosomal recessive familial Mediterranean fever [MIM: 249100]	Stroke, neurocognitive, neurodegenerative, mitochondrial, encephalopathy, aphasia, weakness, muscle jerks, hallucinations, tremors.
175	0	*NPC1*	p.Pro1080IlefsX18	LP	F	autosomal recessive Niemann-Pick disease type C1 (NPC1) [MIM: 257220]	liver failure, hepatitis
175	0	*NPC1*	p.Ser738*	LP	M	autosomal recessive Niemann-Pick disease type C1 (NPC1) [MIM: 257220]	liver failure, hepatitis
176	34	*SETX*	p.Gly2036Arg	LP	M	Amyotrophic lateral sclerosis 4, juvenile [MIM: 602433]; Ataxia-ocular apraxia-2 [MIM: 606002]	ataxia, neuropathy
176	34	*SETX*	Splice defect	LP	F	Amyotrophic lateral sclerosis 4, juvenile [MIM: 602433]; Ataxia-ocular apraxia-2 [MIM: 606002]	ataxia, neuropathy

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177	2	*SLC45A2*	p.Gly89Aspfs*24	LP	F	oculocutaneous albinism type IV [MIM: 606574]	omphalocele, small VSD , AV heart block, developmental delay, cerebellar vermis hypoplasia, oculocutaneous albinism, myopia, optic nerve hypoplasia, ocular albinism
177	2	*SLC45A2*	p.Leu485Pro	LP	M	oculocutaneous albinism type IV [MIM: 606574]	omphalocele, small VSD , AV heart block, developmental delay, cerebellar vermis hypoplasia, oculocutaneous albinism, myopia, optic nerve hypoplasia, ocular albinism
178	0	*ACAD9*	p.Pro616Ser	LP	F	autosomal recessive acyl-CoA dehydrogenase-9 deficiency [MIM: 611126]	lactic acidosis, metabolic acidosis, encephalopathy, developmental delay, emesis
178	0	*ACAD9*	p.Phe120Serfs*9	LP	M	autosomal recessive acyl-CoA dehydrogenase-9 deficiency [MIM: 611126]	lactic acidosis, metabolic acidosis, encephalopathy, developmental delay, emesis
179	1	*FADD*	p.Ser18*	LP	M	autosomal recessive recurrent infections with encephalopathy, hepatic dysfunction; cardiovascular malformations [MIM: 613759]	seizures, stroke, ataxia, hepatomegaly, skin rash, Alpers syndrome, Mitochondrial encephalomyopathy, lactic acidosis, stroke-like episodes, MELAS
179	1	*FADD*	p.Cys105Arg	LP	F	autosomal recessive recurrent infections with encephalopathy, hepatic dysfunction,; cardiovascular malformations [MIM: 613759]	seizures, stroke, ataxia, hepatomegaly, skin rash, Alpers syndrome, Mitochondrial encephalomyopathy, lactic acidosis, stroke-like episodes, MELAS
180	23	*TTN*	p.Arg32684Thrfs*47	LP	M	autosomal recessive early-onset myopathy [MIM: 611705]; limb-girdle muscular dystrophy type 2J [MIM: 608807]	muscular dystrophy, muscle weakness, rhabdomyolysis, calf pain, myopathy, fatigue
180	23	*TTN*	p.Arg33084*	LP	F	autosomal recessive early-onset myopathy [MIM: 611705]; limb-girdle muscular dystrophy type 2J [MIM: 608807]	muscular dystrophy, muscle weakness, rhabdomyolysis, calf pain, myopathy, fatigue
181	1	*LIPT1*	p.Trp269*	P	F	autosomal recessive lipoylation defect of the 2-ketoacid dehydrogenase complexes	lactic acidosis, metabolic acidosis, respiratory distress, mitochondrial
181	1	*LIPT1*	p.Leu327*	P	M	autosomal recessive lipoylation defect of the 2-ketoacid dehydrogenase complexes	lactic acidosis, metabolic acidosis, respiratory distress, mitochondrial
182	4	*AHI1*	p.Cys854Phe	LP	M	autosomal recessive Joubert's syndrome type 3 [MIM: 608629]	developmental delay, spasticity, seizures, hypertonia, Gastroesophageal reflux disease, Chiari malformation, dental caries

Patient Index	Age	Gene Name	Protein Change	Variant Class	Inherited From	Disease Name	Clinical Indication*
182	4	*AHI1*	p.Ser1123Phe	LP	F	autosomal recessive Joubert's syndrome type 3 [MIM: 608629]	developmental delay, spasticity, seizures, hypertonia, Gastroesophageal reflux disease, Chiari malformation, dental caries
183	6	*MUT*	p.Arg108Cys	P	M	autosomal recessive methylmalonic aciduria [MIM: 251000]	liver failure, methylmalonic aciduria, cryptogenic cirrhosis, failure to thrive, Renal insufficiency, Wilson's Disease
183	6	*MUT*	p.Ala631Glnfs*17	P	F	autosomal recessive methylmalonic aciduria [MIM: 251000]	liver failure, methylmalonic aciduria, cryptogenic cirrhosis, failure to thrive, Renal insufficiency, Wilson's Disease
184	8	*TSFM*	p.Val119Leu	LP	F	autosomal recessive combined oxidative phosphorylation deficiency type 3 (COPD3) [MIM: 61050]	cardiomyopathy, cytochrome oxidase deficiency
184	8	*TSFM*	p.Arg333Trp	P	M	autosomal recessive combined oxidative phosphorylation deficiency type 3 (COPD3) [MIM: 61050]	cardiomyopathy, cytochrome oxidase deficiency
185	0	*LAMA2*	p.Glu175*	P	F	autosomal recessive merosin-deficient muscular dystrophy [MIM: 607855]	pontocerebellar hypoplasia, dysmorphic features, hypotonia, myotonic dystrophy, muscular dystrophy, muscle atrophy, developmental delay,
185	0	*LAMA2*	p.Arg683Serfs*21	P	M	autosomal recessive merosin-deficient muscular dystrophy [MIM: 607855]	pontocerebellar hypoplasia, dysmorphic features, hypotonia, myotonic dystrophy, muscular dystrophy, muscle atrophy, developmental delay,
186	26	*ETFDH*	p.Leu496Pro	LP	M	autosomal recessive glutaric acidemia IIC [MIM: 231680]	metabolic disorder, inborn error of metabolism, rhabdomyolysis, lactic acidosis, hypoglycemia, liver failure, muscle weakness, seizures, epilepsy, elevated liver enzymes, Carnitine palmitoyltransferase II, Carnitine-acylcarnitine translocase, Pompe disease, acute metabolic decompensation
186	26	*ETFDH*	p.Pro456Leu	P	F	autosomal recessive glutaric acidemia IIC [MIM: 231680]	metabolic disorder, inborn error of metabolism, rhabdomyolysis, lactic acidosis, hypoglycemia, liver failure, muscle weakness, seizures, epilepsy, elevated liver enzymes, Carnitine palmitoyltransferase II, Carnitine-acylcarnitine translocase, Pompe disease, acute metabolic decompensation
187	45	*POLR3A*	p.Lys123del	LP	F	autosomal recessive hypomyelinating leukodystrophy-7 [MIM: 607694]	Dementia, Tremor, Parkinsonism, Leukodystrophy
187	45	*POLR3A*	p.Met852Val	LP	M	autosomal recessive	Dementia, Tremor, Parkinsonism,

Patient Index	Age	Gene Name	Protein Change	Variant Class	Inherited From	Disease Name	Clinical Indication*
						hypomyelinating leukodystrophy-7 [MIM: 607694]	Leukodystrophy
Inherited Heterozygous							
188	16	*LDB3*	p.Arg268Cys	LP	M	autosomal dominant myofibrillar myopathy type 4 [MIM: 609452]; autosomal dominant dilated cardiomyopathy type 1C with or without noncompaction of the left ventricular myocardium [MIM: 601493]	ataxia, neuropathy, Charcot Marie Tooth
189	21	*COL3A1*	p.Gln1366*	LP	F	autosomal dominant Ehlers-Danlos syndrome type IV [MIM: 130050]; autosomal dominant Ehlers-Danlos syndrome type III [MIM: 130020]	Ehlers-Danlos, Loeys-Dietz, aortic dissection, hypertrophic heart, connective tissue disease
190	12	*OPA1*	p.Arg711*	LP	F	autosomal dominant optic atrophy type 1 (OPA1) [MIM: 165500]	cone-rod dystrophy, achromatopsia, differentiate colors, color vision, visual acuity
191	14	*TNNI3*	p.Arg170Gly	LP	F	dilated cardiomyopathy type 1FF [MIM: 613286]; type 2A [MIM: 611880]; familial hypertrophic cardiomyopathy type 7 [MIM: 613690]; familial restrictive cardiomyopathy [MIM: 115210]	atrial enlargement, diastolic dysfunction, cardiomyopathy, intestinal malrotation
192	0	*COL1A2*	p.Pro986Leu	LP	M	autosomal dominant osteogenesis imperfecta type II [MIM:166210], type III [MIM: 259420]; type IV [MIM:166220]	bone fractures, osteogenesis imperfecta, osteopenia, Rickets, skeletal dysplasia, vitamin D deficiency
>2 LP/P reported							
193	19	*STAT1*	p.Arg274Trp	P	De novo	chronic mucocutaneous candidiasis-7 (CANDF7) [MIM: 600555]	immunodeficiency, chronic infections, growth failure, hemolytic anemia, hypersplenism, splenomegaly, delayed skeletal maturation, IGF-1 deficiency
193	19	*G6PD*	p.Ser188Phe	P	M	chronic non-spherocytic hemolytic anemia (CNSHA) [MIM: 305900]	immunodeficiency, chronic infections, growth failure, hemolytic anemia, hypersplenism, splenomegaly, delayed skeletal maturation, IGF-1 deficiency
194	5	*DYNC1H1*	p.Arg1567Leu	LP	De novo	autosomal dominant axonal Charot-Marie-Tooth disease type 20 [MIM:614228]; autosomal dominant intellectual disability type 13	congenital anomalies, developmental delay, dysmorphic features, dysmorphic features, epilepsy, hearing loss, lissencephaly, pachygyria, seizures, ventriculomegaly

Patient Index	Age	Gene Name	Protein Change	Variant Class	Inherited From	Disease Name	Clinical Indication*
						[MIM:614563]	
194	5	*OTOF*	p.Lys1310dup	LP	M	autosomal recessive auditory neuropathy; deafness [MIM:601071]	congenital anomalies, developmental delay, dysmorphic features, dysmorphic features, epilepsy, hearing loss, lissencephaly, pachygyria, seizures, ventriculomegaly
194	5	*OTOF*	p.Glu1700Gln	LP	F	autosomal recessive auditory neuropathy; deafness [MIM:601071]	congenital anomalies, developmental delay, dysmorphic features, dysmorphic features, epilepsy, hearing loss, lissencephaly, pachygyria, seizures, ventriculomegaly
194	5	*F8*	p.Glu1057Lys	LP	M	X-linked hemophilia A [MIM:306700]	congenital anomalies, developmental delay, dysmorphic features, dysmorphic features, epilepsy, hearing loss, lissencephaly, pachygyria, seizures, ventriculomegaly
195	5	*F9*	p.Ala279Thr	P	M	X-linked recessive hemophilia B [MIM: 306900]	immunodeficiency, hypogammaglobulinemia, hemophilia, factor IX deficiency, iron deficiency anemia, bleeding disorder
195	5	*TNFRSF13B*	p.Cys104Arg	LP	M	common variable immunodeficiency type 2 [MIM: 240500]	immunodeficiency, hypogammaglobulinemia, hemophilia, factor IX deficiency, iron deficiency anemia, bleeding disorder
Other-CES							
Homozygous							
196	16	*PDE6C*	p.Leu653Pro	LP	?/M	achromatopsia; cone dystrophy type 4 (COD4) [MIM: 613093]	cone dystrophy, cone-rod dystrophy, achromatopsia, color vision, photophobia, peripheral vision, central vision, nystagmus, CLCA
197	50	*RLBP1*	p.Phe96_Phe99del	LP	?/M	autosomal recessive Bothnia retinal dystrophy [MIM: 607475]; autosomal recessive Retinitis punctata albescens [MIM: 136880]	Retinal Dystrophy, Stargardt, Retinitis Punctata Albescens, Renal Disease, renal dysplasia, MELAS syndrome, Cystinuria, Cysteinuria, Proteinuria, Alport, Focal segmental glomerulosclerosis
198	25	*MERTK*	p.Leu731Ser	LP	?/M	autosomal recessive retinitis pigmentosa type 38 [MIM: 613862]	Cone-rod dystrophy, retinopathy, stargardt
Compound Heterozygous							
199	15	*RTEL1*	p.Ile449Thr	LP	Not from M	autosomal recessive dyskeratosis congenita type 5 [MIM:615190]	dyskeratosis congenita, T-cell deficiency, immunodeficiency
199	15	*RTEL1*	p.Arg1010*	LP	M	autosomal recessive dyskeratosis congenita type 5 [MIM:615190]	dyskeratosis congenita, T-cell deficiency, immunodeficiency
200	58	*CNGA1*	p.Arg218*	P	Not from M	autosomal recessive Retinitis Pigmentosa 49 (RP49) [MIM: 613756]	retinitis pigmentosa, hypothyroidism, hypogonadism, hypoalphalipoproteinemia, gout

Patient Index	Age	Gene Name	Protein Change	Variant Class	Inherited From	Disease Name	Clinical Indication*
							Atrial fibrillation, colonic diverticulosis, hypertension, sleep apnea, obesity, vitamin D deficiency alpha 1-antitrypsin deficiency
200	58	*CNGA1*	p.Ser320Phe	P	M	autosomal recessive Retinitis Pigmentosa 49 (RP49) [MIM: 613756]	retinitis pigmentosa, hypothyroidism, hypogonadism, hypoalphalipoproteinemia, gout Atrial fibrillation, colonic diverticulosis, hypertension, sleep apnea, obesity, vitamin D deficiency alpha 1-antitrypsin deficiency
Heterozygous not inherited from the parent sequenced (could be de novo)							
201	19	*NF1*	p.Arg2616*	LP	Not from M	autosomal dominant neurofibromatosis type 1 (NF1) [MIM: 162200]	neurofibromatosis
202	3	*SUFU*	p.Tyr38Thrfs*58	P	Not from M	autosomal dominant desmoplastic medulloblastoma [MIM: 155255]; susceptibility to familial meningioma [MIM: 607174]	cancer susceptibilitys, medulloblastoma, dysmorphic features, macrocephaly, hypertelorism, microtia, clinodactyly
203	9	*GNAS*	p.Gln294*	LP	Not from M	autosomal dominant pseudohypoparathyroidism types Ia (PHP Ia) [MIM: 103580]; Ic (PHP Ic) [MIM: 612462]	developmental delay, short stature, amblyopia, spina bifida occulta, seizures, epilepsy, advanced bone age, shortened metacarpals, vesicoureteral reflux, dysmorphic features, microcephaly
204	1	*PIK3R1*	p.Arg649Trp	P	Not from M	autosomal dominant SHORT syndrome [MIM: 269880]	growth retardation, developmental delay, microcephaly, dysmorphic features, small corpus callosum, SHORT syndrome, joint hypermobility
205	9	*NR5A1*	p.Glu51*	P	Not from M	autosomal dominant sex-limited 46,XY sex reversal 3 [MIM:612965]	sexual development, ambiguous genitalia, androgen insensitivity, 5-alpha-reductase deficiency, learning disabilities
Inherited Heterozygous							
206	18	*NR2E3*	p.Gly56Arg	LP	F	autosomal dominant retinitis pigmentosa (type 37) [MIM: 611131]; enhanced S-cone syndrome [MIM: 268100]	retinitis pigmentosa, nyctalopia, vascular attenuation, intraretinal pigmentation, Retinal pigment epithelium, deafness, hearing loss, usher syndrome
207	8	*NSD1*	Splice defect	LP	M	autosomal dominant Sotos Syndrome [MIM: 117550]	autism, developmental delay, macrocephaly, dysmorphic features, hydronephrosis, umbilical hernia, hyperbilirubinemia, atrial septal defect, exotropia, otitis media, retinopathy, Sotos syndrome

*‘Clinical indication’ indicates keywords, clinical descriptors, and potential diagnoses suggested by the referring physician for a given patient.

eTable 3. List of copy number variants (CNVs) and uniparental disomy (UPD) reported and confirmatory status.

Patient Index‡	Test Option	Age	Gene Name	DNA Change	Disease Name	Clinical Indication*	Comment
34	proband	20	*ASS1*	Heterozygous deletion of exons 1 and 2	autosomal recessive citrullinemia [MIM: 215700]	Citrullinemia, developmental delay, seizures, spasticity, tremor, ataxia	Pending confirmation at an outside lab
208	proband	6	*DMD*	Duplication of exons 3-20	Duchenne Muscular Dystrophy [MIM: 310200]	muscular dystrophy	Confirmed by Microarray
209	proband	24	*HSD17B3*	Homozygous deletion of exon 1	recessive pseudohermaphroditism with gynecomastia in males [MIM: 264300]	Disorders of Sex Development (DSD)	Confirmed at an outside lab
210	trio	0	47 XXY	47 XXY	Klinefelter syndrome	developmental delay, hypotonia, hearing loss, frontal bossing	Confirmed by microarray
211	trio	17	*SH2D1A*	Hemizygous deletion of exon 2	X-linked recessive lymphoproliferative syndrome type 1 [MIM: 308240]	cancer susceptibility, immunodeficiency, Burkitt lymphoma	Confirmed at an outside lab
212	proband	17	15q11.2-q13	a region of homozygosity >5Mb that overlapped with 15q11.2-q13	Prader-Willi Syndrome [MIM: 176270]; Angelman Syndrome [MIM: 105830]	developmental delay, muscular dystrophy, myopathy, mitochondrial, hypotonia, dysphagia, scoliosis, heat intolerance	Confirmed at an outside lab
213	trio	2	*SMN1*	Hemizygous deletion of exon 7	autosomal recessive spinal muscular atrophy [MIM: 253300]	motor delay, hypotonia, muscle weakness, Spinal muscular atrophy	Confirmed at an outside lab

Patient Index‡	Test Option	Age	Gene Name	DNA Change	Disease Name	Clinical Indication*	Comment
214†	proband	52	*PTEN*	Homozygous deletion of exon 4	Bannayan-Riley-Ruvalcaba syndrome [MIM: 153480]; Cowden syndrome 1 [MIM: 158350]; Endometrial carcinoma, somatic [MIM: 608089]; Lhermitte-Duclos syndrome [MIM: 158350]; Macrocephaly/autism syndrome [MIM: 605309]; Malignant melanoma, somatic [MIM: 155600]; PTEN hamartoma tumor syndrome [MIM:]; Squamous cell carcinoma, head and neck, somatic [MIM: 275355]; Thyroid carcinoma, follicular, somatic [MIM: 188470]; VATER association with macrocephaly and ventriculomegaly [MIM: 276950]	joint hypermobility, mitral valve prolapse, mitral valve regurgitation, liver cysts, ovarian cysts, Ehlers-Danlos syndrome, connective tissue disorder, bleeding disorder, vascular abnormalities, Dysphagia, gastric polyps, lipoma, bruise, cancer susceptibility	Not confirmed at an outside lab

‡ Continued from eTable2

† Not included in the conclusive diagnosis group

*‘Clinical indication’ indicates keywords, clinical descriptors, and potential diagnoses suggested by the referring physician for a given patient.

eTable 4. Demographic summary of 814 cases.

	Total		<5 years		5-18 years		>18 years	
	Male (n=453)	Female (n=361)	Male (n=144)	Female (n=110)	Male (n=166)	Female (n=100)	Male (n=143)	Female (n=151)
Proband-CES	177 (40%)	161 (45%)	25 (18%)	25 (23%)	44 (27%)	29 (29%)	108 (76%)	107 (71%)
Trio-CES	238 (53%)	172 (48%)	114 (77%)	76 (68%)	99 (57%)	64 (64%)	25 (18%)	32 (22%)
Other-CES	38 (9%)	28 (8%)	5 (4%)	9 (9%)	23 (14%)	7 (7%)	10 (7%)	12 (8%)

eTable 5. Molecular Diagnosis Rate of Phenotypic Subgroups by Age Group for Other Clinical Exome Sequencing

	Age Groups					
	<5 y		5-18 y		>18 y	
	Rate	% (95% CI)	Rate	% (95% CI)	Rate	% (95% CI)
DD	1/6	17 (1-58)	2/13	15 (3-43)	0/5	0 (0-49)
DD + hypotonia	0/1	0 (0-83)	0/3	0 (0-62)	-	
DD + epilepsy or seizures	0/1	0 (0-83)	1/7	14 (1-53)	0/1	0 (0-83)
DD + dysmorphic features	1/3	33 (6-80)	2/9	22 (5-56)	0/3	0 (0-62)
DD + autism	0/3	0 (0-62)	1/7	14 (1-53)	0/2	0 (0-71)
DD + heart disorder			1/2	50 (9-91)		
Ataxia and related neurological disorders	0/1	0 (0-83)	0/1	0 (0-83)	0/1	0 (0-83)
Muscular dystrophy and related disorders			0/1	0 (0-83)	0/1	0 (0-83)
Cardiomyopathy and arrhythmia	0/2	0 (0-71)				
Cancer predisposition	1/1	100 (17-100)	0/2	0 (0-71)	0/2	0 (0-71)
Disorder of sexual development	0/1	0 (0-83)	1/1	100 (17-100)	0/1	0 (0-83)
Retinal disorders			2/3	67 (20-94)	1/5	20 (2-64)

Abbreviations: CES, clinical exome sequencing; DD, developmental delay.

[a]The other CES group includes cases where only 1 or no parent was sequenced but other family members were sequenced.

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