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Supplemental Data

Preconception Carrier Screening by Genome Sequencing: Results from the Clinical Laboratory

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Supplemental Note: Clinical Report

Carrier Results: Four Known Pathogenic Variants Detected.

Gene	Inheritance	Disease	Prevalence	Variant	Classification
SLC26A4	Autosomal Recessive	Pendred Syndrome/ Non-syndromic Hearing Loss DFNB4 with enlarged vestibular aqueduct	1/500[A]	c.1246A>C, (p.Thr416Pro)	Pathogenic
SPG7	Autosomal Recessive	Spastic Paraplegia 7	2-6/100,000[++]	c.1045G>A, (p.Gly349Ser)	Pathogenic
HBA2	Autosomal Recessive	Alpha Thalassemia	1-5/10,000[+++]	$-\alpha^{3.7}$ (α^{+}- thalassemia)	Pathogenic
HFE	Autosomal Recessive	Hereditary Hemochromatosis	1/200 – 1/1000+	c.845G>A (p.Cys282Tyr)	Pathogenic

+: GeneReviews; ++: Genetics Home Reference; +++: orphan.net – varies with population; A- Generalized prevalence of all deafness and hearing loss

Interpretation:

A sample from this individual was referred to our laboratory for analysis of Next-Generation Genome Sequencing (NGS) and Sanger confirmation of variants identified in carrier screening for: (1) conditions with significantly shortened lifespan; (2) serious conditions; (3) mild conditions; (4) conditions with unpredictable outcomes: and (5) conditions that begin as adults.

One known heterozygous missense variant, c.1246A>C (p.Thr416Pro) (NM_000441.1), was detected in exon 10 of the *SLC26A4* gene of this individual by NGS. This study indicated that this individual is a carrier (i.e. not affected) of a pathogenic variant in the *SLC26A4* gene. The *SLC26A4* gene encodes an anion transporter known as pendrin (OMIM#: 605646). Pathogenic variants in the *SLC26A4* gene are associated with autosomal recessive Pendred Syndrome/ Non- syndromic Hearing Loss DFNB4 with enlarged vestibular aqueduct (MIM#: 274600;600791). Individuals affected with Pendred syndrome experience prelingual onset of severe-to-profound bilateral sensorineural hearing impairment with vestibular dysfunction, temporal bone abnormalities, and enlarged thyroid (goiter). DFNB4 is characterized as nonsyndromic sensorineural hearing impairment, vestibular dysfunction, and enlarged vestibular aqueduct without thyroid defects (GeneReviews: Fatemeh *et al*., 2014, http://www.ncbi.nlm.nih.gov/books/NBK1467/). The prevalence of all hearing loss is 1/500 with a carrier frequency of 1/12. This condition is autosomal recessive and is considered a mild condition. We have confirmed this finding in our laboratory using Sanger sequencing.

One known heterozygous missense variant, c.1045G>A (p.Gly349Ser) (NM_003119.2), was detected in exon 8 of the *SPG7* gene of this individual by NGS. This study indicated that this individual is a carrier (i.e. not affected) of a pathogenic variant in the *SPG7* gene. The *SPG7* gene encodes paraplegin, a component of the m-AAA protease, and an ATP-dependent proteolytic complex of the mitochondrial inner membrane that degrades misfolded proteins and regulates ribosome assembly (MIM# 607259). The disorder, spastic paraplegia 7 is characterized by progressive bilateral lower limb weakness and spasticity, and usually presents in early adulthood. Additional features such as hyperreflexia in the arms, sphincter disturbances, spastic dysarthria, dysphagia, pale optic disks, ataxia, nystagmus, strabismus, decreased hearing, scoliosis, pes cavus, motor and sensory neuropathy, and amyotrophy may be observed (Gene Reviews, Casari G. and Marconi R.: http://www.ncbi.nlm.nih.gov/books/NBK1107/). This condition is autosomal recessive and is considered an adult-onset condition. We have confirmed this finding in our laboratory using Sanger sequencing.

One known whole-gene deletion variant of *HBA2* was detected in this individual by NGS. This study indicated that this individual is a silent carrier (i.e., not affected) of a pathogenic variant for the alpha thalassemia disorder. *HBA1* and *HBA2* genes encode the α-globin chains in the hemoglobin molecule. Hemoglobin, the molecule that carriers oxygen in the red blood cells, is a tetramer that comprises two α-globin and two β-globin chains. The duplicate copies of the α- globin genes (*HBA1* and *HBA2*) are on the same chromosome; therefore a normal individual carries four copies of the α-globin gene (2 on each chromosome; αα/αα). Pathogenic variants in α-globin genes can result in complete deletion of one or more copies of the gene or non-deletion variants (GeneReviews: Origa R *et al*., last update 2013). The loss of α-globin chains as a result of these pathogenic variants leads to α-thalassemia (alpha- thalassemia). Pathogenic variants in both genes on the same chromosome (in *cis*) are associated with α^0 – thalassemia and variants affecting only one gene are associated with α^+ – thalassemia. An individual's genotype can determine if they are: silent carriers (-α/αα); alpha- thalassemia trait (--/αα or – α/- α); HbH disease (--/-α) and Hb Bart's hydrops foetalis (--/--). Clinical symptoms can range from asymptomatic (silent carriers) to severely affected (Hb Bart's hydrops foetalis). α-thalassemia is a common disorder and its prevalence varies among various ethnic groups. According to the WHO, the carrier frequency of α^+ – thalassemia (Heterozygous and homozygous) is approximately 5% in the American population (Modell B and Darlison M, 2008 http://www.who.int/bulletin/volumes/86/6/06-036673-table-T1.html). Alpha – thalassemia is autosomal recessive and is considered a life-span limiting condition. We have confirmed this variant by a multiplex PCR assay.

A well-known heterozygous missense variant, c.845G>A (p.Cys282Tyr) (NM_000410.3), was detected in exon 4 of the *HFE* gene of this individual by NGS. This study indicated that this individual is a carrier (ie., not affected) of a pathogenic variant in the *HFE* gene which causes Hereditary Hemochromatosis (HH, MIM#: 235200). *HFE*- associated Hereditary Hemochromatosis (*HFE*-HH) is a common disorder that is characterized by inappropriately high absorption of iron by the gastrointestinal mucosa. (GeneReviews: Seckington *et al*., 2015, http://www.ncbi.nlm.nih.gov/books/NBK1440/). The prevalence of

HFE-HH is 1/200 to 1/1,000, and the carrier frequency is between 1/8 and 1/16. This is an autosomal recessive disorder and is considered an adult-onset condition.

It is important to understand that next generation genome sequencing is a screening test. This individual could carry a variant not detected by this test, or in genes that are not analyzed (see test limitations). In addition, only known pathogenic and likely pathogenic variants are reported.

Recommendations:
In general, we recommend that the reproductive partner of an individual who is a carrier for an autosomal recessive condition be tested. Genetic counseling is recommended.

Evidence for Variant Interpretations:
c.1246A>C (p.Thr416Pro) in Exon 10 of the *SLC26A4* gene (NM_000441.1, chr7:107330665) is interpreted as Pathogenic.
The c.1246A>G (p.Thr416Pro) missense variant in the *SLC26A4* gene is one of the most common pathogenic variants associated with Pendred Syndrome and Non-syndromic Hearing Loss DFNB4 with enlarged vestibular aqueduct as it has been previously reported in multiple affected individuals (Van Hauwe *et al*. 1998, Ladsous M *et al*., 2014). This indicates that the prevalence of this variant is significantly higher in cases compared with controls. Several *in vitro* functional studies have demonstrated that this variant has a damaging effect on the protein's intracellular localization and function (Rotman-Pikielny P *et al*., 2002; Yoon JS *et al*., 2008; Scott DA *et al*., 2000). This variant was also shown to co-segregate with disease in multiple families (Van Hauwe *et al*. 1998). The frequency of this variant is either absent or below that of the disease allele frequency (Exome Sequencing Project [ESP] = 0.021%, 1000 Genomes = NA, ExAC = 0.0021). Multiple *in silico* algorithms predict this variant to have a deleterious effect GERP = 5.10; CADD = 19.47; PolyPhen = 1; SIFT = 0). Finally, several reputable diagnostic laboratories have reported this variant as Pathogenic. Therefore, this collective evidence supports the classification of the c.1246A>C (p.Thr416Pro) as a recessive Pathogenic variant. We have confirmed this variant by Sanger sequencing.

c.1045G>A (p.Gly349Ser) in Exon 8 of the *SPG7* gene (NM_003119.2 3, chr16: 89598369) is interpreted as Pathogenic.
The c.1045G>A (p.Gly349Ser) variant has been observed in a compound heterozygous state with truncating and missense variants, including the p.A510V variant, in several affected individuals (Choquet K *et al.*, 2016; Bonn *et al.* 2010; Brugman et al. 2008; van Gassen KL *et al*., 2012; Schlipf NA et al., 2011). Moreover, this variant is located in the AAA_core (ATPase) domain of the protein, and using a yeast complementation assay system, Bonn *et al*. (2010) showed this variant inhibited respiratory growth in yeast. The frequency of the c.1045G>A (p.Gly349Ser) variant is below that of the disease allele frequency (absent in 1000 Genome and 0.17% in Exome Sequencing Project [ESP]). This variant was also shown to co-segregate with disease in two families (Choquet K *et al.*, 2016; Bonn *et al.* 2010). Finally, computational algorithms predict this variant to be damaging to the protein (GERP = 5.85; CADD = 29.7; PolyPhen = 1; SIFT = 0). A reputable clinical laboratory has recently classified this variant as Pathogenic. Together, this evidence is consistent with a Pathogenic classification. We have confirmed this variant by Sanger sequencing.

The 3.7kb deletion allele of the *HBA2* gene is interpreted as Pathogenic (α^+ – thalassemia silent carrier).

Individuals who are silent carriers of α – thalassemia have only three functional copies of the α-globin gene. Because the two genes are located between homologous elements within this locus, there are several possible breakpoints for deletions. The most common deletions associated with α^+ – thalassemia heterozygous (silent carrier) are the 3.7 kb deletion or the 4.2 kb deletions (Harteveld CL and Higgs DR, 2010), both of which involve deletion of the *HBA2* gene (GeneReviews: Origa R *et al*., last update 2013). Clinically, these individuals can either be asymptomatic or present with a mild reduction in mean corpuscular volume (MCV), moderate microcytosis and hypochormia (Galanello R and Cao A, 2011). We have confirmed this variant by a multiplex PCR assay.

c.845G>A, p.Cys282Tyr in Exon 4 of the *HFE* gene, (NM_000410.3, chr6: 26093141) is interpreted as Pathogenic.

The c.845G>A (p.Cys282Tyr) missense variant is widely recognized as one of the two most common disease-causing variants in the *HFE* gene. Cys282Tyr homozygotes account for 80-85% of typical patients with Hereditary Hemochromatosis (HH). However, the majority of individuals who are homozygous for this variant do not develop the disease (GeneReviews: Seckington *et al*., 2015, http://www.ncbi.nlm.nih.gov/books/NBK1440/; Ramrakhiani S, Bacon BR., 1998, Morrison ED *et al*., 2003). In summary, this variant c.845G>A (p.Cys282Tyr) meets our criteria for a recessive Pathogenic classification. We have confirmed this finding in our laboratory using Sanger sequencing.

Method:

Next-generation genome sequencing was performed in the Illumina CLIA laboratory. Genomic DNA was prepped with TruSeq DNA LT and then sequenced on a HiSeq 2000 or 2500 (Illumina, version 3 chemistry) with 100bp paired-end reads. Resulting sequences were aligned to the human genome reference (hg19) using the Burrows-Wheeler Aligner (BWA) and variants identified with the Genome Analysis Toolkit (GATK) at the University of Washington (UW). A modified version of the SeattleSeq tool was used to annotate variants found within a defined set of colon cancer and actionable genes. OHSU laboratory analyzed the annotated variant list to identify pathogenic variants in the attached gene list for evaluation of carrier status. For confirmation studies, genomic DNA was extracted in our laboratory using the Puregene extraction method, and pathogenic variants were confirmed by custom designed Sanger sequencing. The sequence was assembled and analyzed in comparison to the published reference sequence for each gene in which a pathogenic variant was identified. Only known pathogenic and likely pathogenic variants were confirmed and reported.

The NGS data was also assessed for the average depth of coverage and data quality threshold values:

Mean Depth of Coverage[1]	42.7X
Quality threshold[2]	87.73%

[1]Mean depth of coverage refers to the sequence mean read depth across the genome.

[2]The quality threshold refers to the percentage of the genome where read depth was at least 30X coverage to permit high quality variant base calling, annotation and evaluation. Average quality threshold is 87.73% at >=30X of the genome, indicating that a small portion of the target region may not be covered with sufficient depth or quality to call variant positions confidently.

***HBA2* – gene deletion assay:**

A multiplex PCR assay, as described by Liu YT *et al*., (2000) was used to determine deletions at the alpha thalassemia locus.

List of Carrier Status Genes Covered at Less Than 10X Read Depth:

1. Survival Motor Neuron 1: *SMN1*
2. Hemoglobin, alpha 2: *HBA2*

Limitations:

1. This assay has limited ability to detect large deletions or duplications as well as small insertions and deletions.
2. This test also has limited ability to detect mosaicism.
3. This test does not provide complete coverage of all coding exons.
4. Noncoding regions may have limited information and limited ability to interpret.
5. The assay does not detect variants located:
    a. in regions of insufficient coverage,
    b. in regions containing paralogous genes or pseudogenes,
    c. in regions where the reference genome is inaccurate or contains gaps and insertions,
    d. in regions of high GC content
6. All identified variants of uncertain significance are not reported.
7. Genes not associated clinically with Mendelian disorders at the time this test was performed were not analyzed.
8. Genes not analyzed.

References:

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Genes and Associated Diseases:

CATEGORY: LIFESPAN LIMITING

AARS2- COMBINED OXIDATIVE PHOSPHORYLATION DEFICIENCY 8, ***ABCA12***- ICHTHYOSIS CONGENITA, HARLEQUIN FETUS, ***ACAD9***- MITOCHONDRIAL COMPLEX I DEFICIENCY DUE TO ACAD9 DEFICIENCY, ***ACE***- RENAL TUBULAR DYSGENESIS, ***ACOX1***- PEROXISOMAL ACYL-COA OXIDASE DEFICIENCY, ***AGPS***- RHIZOMELIC CHONDRODYSPLASIA PUNCTATA,3, ***AGT***- RENAL TUBULAR DYSGENESIS, ***AGTR1***- RENAL TUBULAR DYSGENESIS, ***ALG1***- CONGENITAL DISORDER OF GLYCOSYLATION,IK, ***AMACR***- BILE ACID SYNTHESIS DEFECT,CONGENITAL,4, ***AMT***- GLYCINE ENCEPHALOPATHY, ***ARX***- CORPUS CALLOSUM AGENESIS OF WITH ABNORMAL GENITALIA; EPILEPTIC ENCEPHALOPATHY,EARLY INFANTILE,1; LISSENCEPHALY, X-LINKED, 2, ***ATP7A***- MENKES DISEASE, ***ATPAF2***- MITOCHONDRIAL COMPLEX V (ATP SYNTHASE) DEFICIENCY, NUCLEAR TYPE 1, ***B9D1***- MECKEL SYNDROME 9, ***B9D2***- MECKEL SYNDROME 10, ***BCS1L***- GRACILE SYNDROME; MITOCHONDRIALCOMPLEX III DEFICIENCY, ***C5ORF42***- JOUBERT SYNDROME 17, ***CC2D2A***- COACH SYNDROME; JOUBERT SYNDROME 9; MECKEL SYNDROME, TYPE 6, ***CDKL5***- EPILEPTIC ENCEPHALOPATHY,EARLY INFANTILE,2, ***CEP290***- JOUBERT SYNDROME 5; LEBER CONGENITAL AMAUROSIS 10; MECKEL SYNDROME, TYPE 4, ***CHRNA1***- MULTIPLE PTERYGIUM SYNDROME, LETHAL, ***CHRND***- MULTIPLE PTERYGIUM SYNDROME, LETHAL, ***CHRNG***- MULTIPLE PTERYGIUM SYNDROME, LETHAL, ***CLN6***- CEROID LIPOFUSCINOSIS, NEURONAL,6, ***CNTN1***- MYOPATHY, CONGENITAL, COMPTON-NORTH, ***COQ6***- COENZYME Q10 DEFICIENCY, PRIMARY, 6, ***COQ9***- COENZYME Q10 DEFICIENCY, PRIMARY, 5, ***COX10***- LEIGH SYNDROME, ***COX15***- CARDIOENCEPHALOMYOPATHY, FATAL INFANTILE, DUE TO CYTOCHROME C OXIDASE DEFICIENCY 2, ***CPT1A***- CARNITINE PALMITOYLTRANSFERASE DEFICIENCY 1A, ***CRTAP***- OSTEOGENESIS IMPERFECTA, TYPE VII, ***CTSD***- CEROIDLIPOFUSCINOSIS,NEURONAL, 10, ***DCX***- LISSENCEPHALY1, ***DGUOK***- MITOCHONDRIAL DNA DEPLETION SYNDROME 3, ***DNAJC19***- 3-METHYLGLUTACONIC ACIDURIA,V, ***DOK7***- FETAL AKINESIA DEFORMATION SEQUENCE, ***DOLK***- CONGENITAL DISORDER OF GLYCOSYLATION, IM, ***DSP***- EPIDERMOLYSIS BULLOSA, LETHAL ACANTHOLYTIC, ***EFEMP2***- CUTIS LAXA, TYPE IB, ***EIF2AK3***- MULTIPLE EPIPHYSEAL DYSPLASIAWITH EARLY ONSET DIABETES MELLITUS, ***ENPP1***- ARTERIAL CALCIFICATION, GENERALIZED,OF INFANCY, ***ERBB3***- LETHAL CONGENITAL CONTRACTURE SYNDROME 2, ***ERCC6***- CEREBROOCULOFACIOSKELETAL SYNDROME1; COCKAYNE SYNDROME,B, ***ERCC8***- COCKAYNE SYNDROME,A, ***ESCO2***- ROBERTS SYNDROME, ***ETFA***- MULTIPLE ACYL-COA DEHYDROGENASE DEFICIENCY, ***ETFB***- MULTIPLE ACYL-COA DEHYDROGENASE DEFICIENCY, ***ETFDH***- MULTIPLE ACYL-COA DEHYDROGENASE DEFICIENCY, ***ETHE1***- ETHYLMALONIC ENCEPHALOPATHY, ***FANCB***- FANCONI ANEMIA, COMPLEMENTATION GROUP B, ***FAM20C***- RAINE SYNDROME, ***FARS2***-

COMBINED OXIDATIVE PHOSPHORYLATION DEFICIENCY 14, ***FBLN5***- CUTIS LAXA,IA, ***PKHD1***- POLYCYSTIC KIDNEY DISEASE, AUTOSOMAL RECESSIVE, ***FGFR2***- ANTLEY-BIXLER SYNDROME WITHOUT GENITAL ANOMALIES OR DISORDERED STEROIDOGENESIS, ***FH***- FUMARASE DEFICIENCY, ***FKTN***- MUSCULAR DYSTROPHY-DYSTROGLYCANOPATHY (CONGENITAL WITH BRAIN AND EYE ANOMALIES), TYPE A, ***FOXP3***- IMMUNODYSREGULATION, POLYENDOCRINOPATHY, AND ENTEROPATHY, ***GALC***- KRABBE DISEASE, ***GFM1***- COMBINED OXIDATIVE PHOSPHORYLATION DEFICIENCY 1, ***GLB1***- GM1-GANGLIOSIDOSIS, TYPE I, ***GLE1***- LETHAL CONGENITAL CONTRACTURE SYNDROME1, ***GNPTAB***- MUCOLIPIDOSIS II ALPHA/BETA, ***GUSB***- MUCOPOLYSACCHARIDOSIS VII, ***HBA1***- ALPHA THALASSEMIA, ***HBA2***- ALPHA THALASSEMIA, ***HEXA***- TAY-SACHS DISEASE, ***HIBCH***- 3-HYDROXYISOBUTYRYL-COA HYDROLASE DEFICIENCY, ***HSD17B4***- D-BIFUNCTIONAL PROTEIN DEFICIENCY, ***HSPG2***- DYSSEGMENTAL DYSPLASIA, SILVERMAN-HANDMAKER TYPE, ***HYLS1***- HYDROLETHALUS SYNDROME 1, ***IDUA***- HURLER SYNDROME, ***IGHMBP2***- SPINAL MUSCULAR ATROPHY, DISTAL,1, ***IKBKG***- ECTODERMAL DYSPLASIA, ANHIDROTIC, WITH IMMUNODEFICIENCY, OSTEOPETROSIS, AND LYMPHEDEMA, ***INSR***- DONOHUE SYNDROME, ***INVS***- NEPHRONOPHTHISIS 2, ***ITGA6***- EPIDERMOLYSIS BULLOSA JUNCTIONALIS WITH PYLORIC ATRESIA, ***ITGB4***- EPIDERMOLYSIS BULLOSA JUNCTIONALIS WITH PYLORIC ATRESIA, ***KLHL40***- NEMALINE MYOPATHY 8, ***LAMA3***- EPIDERMOLYSIS BULLOSA, JUNCTIONAL, NONHERLITZ, ***LAMB2***- PIERSON SYNDROME, ***LAMB3***- EPIDERMOLYSIS BULLOSA, JUNCTIONAL, NONHERLITZ, ***LAMC2***- EPIDERMOLYSIS BULLOSA, JUNCTIONAL,NONHERLITZ, ***LBR***- GREENBERG DYSPLASIA, ***LIAS***- PYRUVATE DEHYDROGENASE LIPOIC ACID SYNTHETASE DEFICIENCY, ***LIFR***- STUVE-WIEDEMANN SYNDROME, ***LMNA***- RESTRICTIVE DERMOPATHY, LETHAL, ***LRPPRC***- LEIGH SYNDROME,FRENCH CANADIAN, ***MKS1***- BARDET-BIEDL SYNDROME 13; MECKEL SYNDROME,1, ***MOCS1***- MOLYBDENUM COFACTOR DEFICIENCY, COMPLEMENTATION GROUP A, ***MOCS2***- MOLYBDENUM COFACTOR DEFICIENCY, COMPLEMENTATION GROUP B, ***MPL***- AMEGAKARYOCYTIC THROMBOCYTOPENIA,CONGENITAL, ***MRPS22***- COMBINED OXIDATIVE PHOSPHORYLATION DEFICIENCY 5, ***MYO5A***- ELEJALDE DISEASE; GRISCELLI SYNDROME,1, ***NDUFA11***- MITOCHONDRIAL COMPLEX I DEFICIENCY, ***NDUFAF2***- MITOCHONDRIAL COMPLEX I DEFICIENCY, ***NDUFAF3***- MITOCHONDRIAL COMPLEX I DEFICIENCY, ***NDUFAF4***- MITOCHONDRIAL COMPLEX I DEFICIENCY, ***NDUFAF6***- LEIGH SYNDROME, ***NDUFB3***- MITOCHONDRIAL COMPLEX I DEFICIENCY, ***NDUFS1***- MITOCHONDRIAL COMPLEX I DEFICIENCY, ***NDUFS2***- MITOCHONDRIAL COMPLEX I DEFICIENCY, ***NDUFS4***- LEIGH SYNDROME, ***NDUFS6***- MITOCHONDRIAL COMPLEX I DEFICIENCY, ***NDUFS7***- LEIGH SYNDROME, ***NDUFS8***- LEIGH SYNDROME, ***NDUFV1***- MITOCHONDRIAL COMPLEX I DEFICIENCY, ***NFU1***- MULTIPLE MITOCHONDRIAL DYSFUNCTIONS SYNDROME 1, ***NPHP3***- RENAL-HEPATIC-PANCREATIC DYSPLASIA 1, ***OFD1***- OROFACIODIGITAL SYNDROME I; SIMPSON-GOLABI-BEHMEL SYNDROME, TYPE 2, ***OSTM1***- OSTEOPETROSIS, AUTOSOMAL RECESSIVE 5, ***P3H1***- OSTEOGENESIS IMPERFECTA,VIII, ***PC***- PYRUVATE CARBOXYLASE DEFICIENCY, ***PDHA1***- PYRUVATE DEHYDROGENASE E1-ALPHA DEFICIENCY, ***PDHB***- PYRUVATE DEHYDROGENASE E1-BETA DEFICIENCY, ***PDSS1***- COENZYME Q10 DEFICIENCY, PRIMARY, 2, ***PDSS2***- COENZYME Q10 DEFICIENCY, PRIMARY, 3, ***PEX1***- PEROXISOME BIOGENESIS DISORDER 1A (ZELLWEGER), ***PEX7***- RHIZOMELIC CHONDRODYSPLASIA PUNCTATA, TYPE 1, ***PLA2G6***- NEURODEGENERATION WITH BRAIN IRON ACCUMULATION 2A, ***PLEC***- EPIDERMOLYSIS BULLOSA SIMPLEX WITH MUSCULAR DYSTROPHY, ***POMT1***- MUSCULAR DYSTROPHY-DYSTROGLYCANOPATHY (CONGENITAL WITH BRAIN AND EYE ANOMALIES), TYPE A, 1, ***POR***- ANTLEY-BIXLER SYNDROME WITH GENITAL ANOMALIES AND DISORDERED STEROIDOGENESIS, ***PPT1***- NEURONAL CEROID LIPOFUSCINOSIS 1, ***PRF1***- HEMOPHAGOCYTIC LYMPHOHISTIOCYTOSIS, FAMILIAL, 2, ***PRKAG2***- GLYCOGEN STORAGE DISEASE OF HEART,LETHAL CONGENITAL, ***PROP1***- PITUITARY HORMONE DEFICIENCY, COMBINED, 2, ***PSAP***- COMBINED SAPOSIN DEFICIENCY; KRABBE DISEASE,ATYPICAL,DUE TO SAPOSIN A DEFICIENCY; METACHROMATIC LEUKODYSTROPHY DUE TO SAPOSIN B DEFICIENCY, ***PTH1R***- CHONDRODYSPLASIA, BLOMSTRAND TYPE, ***RARS2***- PONTOCEREBELLAR HYPOPLASIA, TYPE 6, ***REN***- RENAL TUBULAR DYSGENESIS, ***RMND1***- COMBINED OXIDATIVE PHOSPHORYLATION DEFICIENCY 11, ***RPGRIP1L***- MECKEL SYNDROME, TYPE 5, ***RRM2B***- MITOCHONDRIAL DNA DEPLETION SYNDROME 8A (ENCEPHALOMYOPATHIC TYPE WITH RENAL TUBULOPATHY), ***SARS2***- HYPERURICEMIA, PULMONARY HYPERTENSION, RENAL FAILURE, AND ALKALOSIS SYNDROME, ***SCO1***- MITOCHONDRIAL COMPLEX IV DEFICIENCY, ***SCO2***- CARDIOENCEPHALOMYOPATHY, FATAL INFANTILE, DUE TO CYTOCHROME C OXIDASE DEFICIENCY 1, ***SDHA***- CARDIOMYOPATHY,

DILATED, 1GG; LEIGH SYNDROME; MITOCHONDRIAL RESPIRATORY CHAIN COMPLEX II DEFICIENCY, ***SLC17A5***- INFANTILE SIALIC ACID STORAGE DISEASE, ***SLC25A22***- EPILEPTIC ENCEPHALOPATHY,EARLY INFANTILE,3, ***SLC25A3***- MITOCHONDRIAL PHOSPHATE CARRIER DEFICIENCY, ***SLC26A2***- ACHONDROGENESIS, TYPE IB; ATELOSTEOGENESIS,II, ***SLC35D1***- SCHNECKENBECKEN DYSPLASIA, ***SMN1***- SPINAL MUSCULAR ATROPHY 1; SPINAL MUSCULAR ATROPHY 2; SPINAL MUSCULAR ATROPHY 3; SPINAL MUSCULAR ATROPHY 4, ***SMPD1***- NIEMANN-PICK TYPE A, ***SNAP29***- CEREBRAL DYSGENESIS, NEUROPATHY, ICHTHYOSIS, AND PALMOPLANTAR KERATODERMA SYNDROME, ***STRA6***- MICROPHTHALMIA, SYNDROMIC 9, ***SUCLG1***- MITOCHONDRIAL DNA DEPLETION SYNDROME 9 (ENCEPHALOMYOPATHIC TYPE WITH METHYLMALONIC ACIDURIA), ***SURF1***- LEIGH SYNDROME, ***TAZ***- BARTH SYNDROME, ***TCIRG1***- OSTEOPETROSIS,AR1, ***TCTN3***- OROFACIODIGITAL SYNDROME IV, ***TK2***- MITOCHONDRIAL DNA DEPLETION SYNDROME,MYOPATHIC, ***TMEM231***- JOUBERT SYNDROME 20; MECKEL SYNDROME 11, ***TMEM237***- JOUBERT SYNDROME 14, ***TMEM70***- MITOCHONDRIAL COMPLEX V (ATP SYNTHASE) DEFICIENCY, NUCLEAR TYPE 2, ***TPP1***- CEROID LIPOFUSCINOSIS, NEURONAL, 2, ***TSEN54***- PONTOCEREBELLAR HYPOPLASIA, TYPE 5; PONTOCEREBELLAR HYPOPLASIA TYPE 2A; PONTOCEREBELLAR HYPOPLASIA TYPE 4, ***TSFM***- COMBINED OXIDATIVE PHOSPHORYLATION DEFICIENCY 3, ***TSPYL1***- SUDDEN INFANT DEATH WITH DYSGENESIS OF THE TESTES SYNDROME, ***UBA1***- SPINAL MUSCULAR ATROPHY, X-LINKED 2, ***UBR1***- JOHANSON BLIZZARD SYNDROME, ***VPS33B***- ARTHROGRYPOSIS, RENAL DYSFUNCTION, AND CHOLESTASIS 1, ***WAS***- WISKOTT ALDRICH SYNDROME; NEUTROPENIA, SEVERE CONGENITAL, X-LINKED; THROMBOCYTOPENIA 1, ***ZMPSTE24***- RESTRICTIVE DERMOPATHY, LETHAL

CATEGORY: SERIOUS

AAAS- ACHALASIA-ADDISONIANISM-ALACRIMA-SYNDROME, ***ABCB11***- CHOLESTASIS, PROGRESSIVE FAMILIAL INTRAHEPATIC2, ***ABCB7***- ANEMIA, SIDEROBLASTIC, AND SPINOCEREBELLAR ATAXIA, ***ABCC8***- FAMILIAL HYPERINSULINEMIA, ***ABCD1***- ADRENOLEUKODYSTROPHY, ***ABHD5***- CHANARIN-DORFMAN SYNDROME(ICHTHYOTIC NEUTRAL LIPID STORAGE DISEASE), ***ACADM***- MEDIUM-CHAIN ACYL-COA DEHYDROGENASE DEFICIENCY, ***ACADVL***- VERY LONG-CHAIN ACYL-COA DEHYDROGENASE DEFICIENCY, ***ACO2***- INFANTILE CEREBELLAR-RETINAL DEGENERATION, ***ADA***- SEVERE COMBINED IMMUNODEFICIENCY, T CELL-NEGATIVE, ***ADAMTS13***- THROMBOTIC THROMBOCYTOPENIC PURPURA,CONGENITAL, ***ADAMTS2***- EHLERS DANLOS SYNDROME, VII, ***ADAMTSL2***- GELEOPHYSIC DYSPLASIA, ***ADGRV1***- USHER SYNDROME, IIC, ***AFG3L2***- SPASTIC ATAXIA 5, ***AGA***- SPARTYLGLYCOSAMINURIA, ***AGK***- SENGERS SYNDROME, ***AGL***- GLYCOGEN STORAGE DISEASE III, ***AGXT***- HYPEROXALURIA, PRIMARY, TYPE I, ***AHI1***- JOUBERT SYNDROME 3, ***AIPL1***- LEBER CONGENITAL AMAUROSIS 4, ***AIRE***- AUTOIMMUNE POLYENDOCRINE SYNDROME, TYPE I, +/- REVERSIBLE METAPHYSEAL DYSPLASIA, ***ALDH3A2***- SJOGREN-LARSSON SYNDROME, ***ALDH5A1***- SUCCINIC SEMI ALDEHYDE DEHYDROGENASE DEFICIENCY, ***ALG6***- CONGENITAL DISORDER OF GLYCOSYLATION IC, ***ALMS1***- ALSTROM SYNDROME, ***ALOX12B***- ICHTHYOSIS, CONGENITAL, 2, ***ALPL***- HYPOPHOSPHATASIA, INFANTILE, ***ALS2***- AMYOTROPHIC LATERAL SCLEROSIS 2,JUVENILE; PRIMARY LATERAL SCLEROSIS,JUVENILE, ***AP3B1***- HERMANSKY-PUDLAK SYNDROME 2, ***APTX***- ATAXIA,EARLY ONSET,WITH OCULOMOTOR APRAXIA AND HYPOALBUMINEMIA, ***ARL13B***- JOUBERT SYNDROME 8, ***ARL6***- BARDET-BIEDL SYNDROME 3, ***ARSA***- METACHROMATIC LEUKODYSTROPHY, ***ARSB***- MUCOPOLYSACCHARIDOSIS VI, ***ARSE***- CHONDRODYSPLASIA PUNCTATA 1, ***ASL***- ARGININOSUCCINIC ACIDURIA, ***ASPA***- CANAVAN, ***ASS1***- CITRULLINEMIA TYPE 1, ***ATM***- ATAXIA TELANGIECTASIA, ***ATP13A2***- KUFOR-RAKEB SYNDROME, ***ATP5E***- MITOCHONDRIAL COMPLEX V (ATP SYNTHASE) DEFICIENCY, NUCLEAR TYPE 3, ***ATP6V0A2***- CUTIS LAXA II, ***ATP7B***- WILSON DISEASE, ***ATP8B1***- CHOLESTASIS, ROGRESSIVE FAMILIAL INTRAHEPATIC 1, ***ATR***- SECKEL SYNDROME 1, ***ATRX***- THALASSEMIA/MENTAL ETARDATION SYNDROME,NONDELETION, ***AVP***- DIABETES INSIPIDUS, NEUROHYPOPHYSEAL, ***B4GALT1***- CONGENITAL DISORDER OF GLYCOSYLATION, IID, ***BBS1***- BARDET-BIEDL SYNDROME 1, ***BBS10***- BARDET-BIEDL SYNDROME 10, ***BBS12***- BARDET-BIEDL SYNDROME 12, ***BBS2***- BARDET-BIEDL SYNDROME 2, ***BBS4***- BARDET-BIEDL SYNDROME 4, ***BBS5***- BARDET-BIEDL SYNDROME 5, ***BBS7***- BARDET-BIEDL SYNDROME 7, ***BCKDHA***- MAPLE SYRUP URINE DISEASE IA, ***BCKDHB***- MAPLE SYRUP URINE DISEASE, CLASSIC, IB, ***BRCA2***- FANCONI ANEMIA, COMPLEMENTATION GROUP D1, ***MPC1***- MITOCHONDRIAL PYRUVATE CARRIER DEFICIENCY, ***BTD***- BIOTINIDASE DEFICIENCY, ***BTK***- AGAMMAGLOBULINEMIA, ***C10ORF2***-

PERRAULT SYNDROME 5; MITOCHONDRIAL DNA DEPLETION SYNDROME 7 (HEPATOCEREBRAL TYPE), ***C12ORF65***- SPASTIC PARAPLEGIA 55; COMBINED OXIDATIVE PHOSPHORYLATION DEFICIENCY 7, ***CA2***- OSTEOPETROSIS, 3, ***CBS***- HOMOCYSTINURIA DUE TO CYSTATHIONINE BETA-SYNTHASE DEFICIENCY, ***CD40LG***- IMMUNODEFICIENCY WITH HYPER IGM, 1, ***CDH23***- DEAFNESS 12; USHER SYNDROME, ID, ***CEP41***- JOUBERT SYNDROME 15, ***CFP***- PROPERDIN DEFICIENCY, ***CFTR***- CYSTIC FIBROSIS, ***CHKB***- MUSCULAR DYSTROPHY, CONGENITAL, MEGACONIAL TYPE, ***CHM***- CHOROIDEREMIA, ***CHRNE***- CONGENITAL MYASTHENIC SYNDROME, ***CHRNG***- MULTIPLE PTERYGIUM SYNDROME, ESCOBAR, ***CISD2***- WOLFRAM SYNDROME 2, ***CLDN1***- ICHTHYOSIS, LEUKOCYTE VACUOLES, ALOPECIA, AND SCLEROSING CHOLANGITIS, ***CLDN14***- DEAFNESS 29, ***CLDN19***- HYPOMAGNESEMIA,RENAL,WITH OCULAR INVOLVEMENT, ***CLN3***- CEROID LIPOFUSCINOSIS,NEURONAL 3, ***CLN5***- CEROID LIPOFUSCINOSIS, EURONAL, 5, ***CLN8***- CEROID LIPOFUSCINOSIS, NEURONAL, 8, NORTHERN EPILEPSY VARIANT, ***CLRN1***- RETINITIS PIGMENTOSA 61; USHER SYNDROME, III, ***COL17A1***- EPIDERMOLYSIS BULLOSA, JUNCTIONAL, NONHERLITZ, ***COL1A2***- EHLERS DANLOS SYNDROME, CARDIAC VALVULAR, ***COL4A3***- ALPORT SYNDROME, ***COL4A4***- ALPORT SYNDROME, ***COL4A5***- ALPORT SYNDROME, ***COL6A1***- ULLRICH CONGENITAL MUSCULAR DYSTROPHY 1; BETHLEM MYOPATHY 1, ***COL6A2***- ULLRICH CONGENITAL MUSCULAR DYSTROPHY 1; ETHLEM MYOPATHY 1, ***COL6A3***- ULLRICH CONGENITAL MUSCULAR DYSTROPHY 1; BETHLEM MYOPATHY 1, ***COL7A1***- EPIDERMOLYSIS BULLOSA DYSTROPHICA, ***COX20***- MITOCHONDRIAL COMPLEX IV DEFICIENCY, ***CPS1***- CARBAMOYL PHOSPHATE SYNTHETASE 1 DEFICIENCY, HYPERAMMONEMIA, ***CRLF1***- COLD-INDUCED SWEATING SYNDROME 1, ***CRX***- LEBER CONGENITAL AMAUROSIS 7, ***CSTB***- MYOCLONIC EPILEPSY OF UNVERRICHT AND LUNDBORG, ***CTNS***- CYSTINOSIS, NEPHROPATHIC, ***CTSK***- PYCNODYSOSTOSIS, ***CYP17A1***- CONGENITAL ADRENAL HYPERPLASIA, , DUE TO 17-ALPHA-HYDROXYLASE DEFICIENCY, ***CYP21A2***- CONGENITAL ADRENAL HYPERPLASIA ,DUE TO 21-HYDROXYLASE DEFICIENCY, ***D2HGDH***- D-2-HYDROXYGLUTARIC ACIDURIA, ***NROB1***- ADRENAL HYPOPLASIA, CONGENITAL, ***DCAF17***- WOODHOUSE-SAKATI SYNDROME, ***DCLRE1C***- OMENN SYNDROME, ***DDB2***- XERODERMA PIGMENTOSUM, COMPLEMENTATION GROUP E, ***DDC***- AROMATIC L-AMINO ACID DECARBOXYLASE DEFICIENCY, ***DFNB31***- USHER SYNDROME, TYPE IID, ***DFNB59***- DEAFNESS 59, ***DHCR24***- DESMOSTEROLOSIS, ***DHCR7***- SMITH-LEMLI-OPITZ SYNDROME, ***DKC1***- DYSKERATOSIS CONGENITA, ***DLAT***- PYRUVATE DEHYDROGENASE E2 EFICIENCY, ***DLD***- DIHYDROLIPOAMIDE DEHYDROGENASE DEFICIENCY, ***DLL3***- SPONDYLOCOSTAL YSOSTOSIS 1, ***DMD***- MUSCULAR DYSTROPHY, DUCHENNE TYPE; CARDIOMYOPATHY, DILATED, 3B, ***DMP1***- HYPOPHOSPHATEMIC RICKETS, ***DNMT3B***- IMMUNODEFICIENCY CENTROMERIC INSTABILITY FACIAL ANOMALIES SYNDROME, ***DPAGT1***- CONGENITAL DISORDER OF GLYCOSYLATION, IJ, ***DPM1***- CONGENITAL DISORDER OF GLYCOSYLATION, IE, ***DPYD***- DIHYDROPYRIMIDINE DEHYDROGENASE DEFICIENCY, ***DSP***- SKIN FRAGILITY WOOLLY HAIR SYNDROME, ***DTNBP1***- HERMANSKY-PUDLAK SYNDROME 7, ***DYNC2H1***- SHORT-RIB THORACIC DYSPLASIA 3 +/- POLYDACTYLY, ***EARS2***- COMBINED OXIDATIVE PHOSPHORYLATION DEFICIENCY 12, ***EGR2***- HYPERTROPHIC NEUROPATHY OF DEJERINE SOTTAS; NEUROPATHY, CONGENITAL HYPOMYELINATING OR AMYELINATING, ***EMD***- EMERY-DREIFUSS MUSCULAR DYSTROPHY 1, ***EPM2A***- MYOCLONIC EPILEPSY OF LAFORA, ***ERCC2***- TRICHOTHIODYSTROPHY 1, PHOTOSENSITIVE; XERODERMA PIGMENTOSUM,COMPLEMENTATION GROUP D, ***ERCC3***- XERODERMA PIGMENTOSUM, COMPLEMENTATION GROUP B, ***ERCC4***- XERODERMA PIGMENTOSUM, COMPLEMENTATION GROUP F, ***ERCC5***- XERODERMA PIGMENTOSUM, COMPLEMENTATION GROUP G , ***ERCC6***- DE SANCTIS-CACCHIONE SYNDROME, ***ESPN***- DEAFNESS 36, +/- VESTIBULAR INVOLVEMENT, ***ESRRB***- DEAFNESS 35, ***EVC***- ELLIS-VAN CREVELD SYNDROME, ***F8***- HEMOPHILIA A (FACTOR VIII), ***FAH***- TYROSINEMIA, TYPE I, ***FAM126A***- LEUKODYSTROPHY,HYPOMYELINATING, 5, ***FANCA***- FANCONI ANEMIA COMPLEMENTATION GROUP A, ***FBP1***- FRUCTOSE-1,6-BISPHOSPHATASE DEFICIENCY, ***FECH***- PROTOPORPHYRIA, ERYTHROPOIETIC, ***FLNA***- INTESTINAL PSEUDOOBSTRUCTION, NEURONAL, CHRONIC IDIOPATHIC, ***FMR1***- FRAGILE X MENTAL RETARDATION SYNDROME, ***FOXN1***- TCELL IMMUNODEFICIENCY,CONGENITAL ALOPECIA,AND NAIL DYSTROPHY, ***FOXRED1***- LEIGH SYNDROME, ***FRAS1***- FRASER SYNDROME, ***FREM2***- FRASER SYNDROME, ***FUCA1***- FUCOSIDOSIS, ***FXN***- FRIEDREICH ATAXIA 1, ***G6PC***- GLYCOGEN STORAGE DISEASE IA, ***GAA***- GLYCOGEN STORAGE DISEASE II (POMPE), ***GALT***- GALACTOSEMIA, ***GATA1***- ANEMIA, +/- NEUTROPENIA AND/OR PLATELET ABNORMALITIES; THROMBOCYTOPENIA WITH BETA-THALASSEMIA; THROMBOCYTOPENIA, +/- DYSERYTHROPOIETIC ANEMIA, ***GBE1***- GLYCOGEN STORAGE DISEASE

IV, ***GCDH***- GLUTARIC ACIDEMIA I, ***GCSH***- GLYCINE ENCEPHALOPATHY, ***GIPC3***- DEAFNESS 15, ***GJB3***- DEAFNESS 1A, ***GJB6***- DEAFNESS1B, ***GJC2***- LEUKODYSTROPHY,HYPOMYELINATING, 2, ***GLA***- FABRY DISEASE, ***GLB1***- GM1-GANGLIOSIDOSIS, TYPE II, ***GLDC***- GLYCINE ENCEPHALOPATHY, ***GNPTAB***- MUCOLIPIDOSIS III ALPHA/BETA, ***GNS***- MUCOPOLYSACCHARIDOSIS IIID, ***GPR56***- POLYMICROGYRIA, BILATERAL FRONTOPARIETAL, ***GPR98***- USHER SYNDROME TYPE IIC, ***GPSM2***- CHUDLEY-MCCULLOUGH SYNDROME, ***GRHPR***- HYPEROXALURIA, PRIMARY, TYPE II, ***GRXCR1***- DEAFNESS, 25, ***GSS***- GLUTATHIONE SYNTHETASE DEFICIENCY, ***GTF2H5***- TRICHOTHIODYSTROPHY 3, PHOTOSENSITIVE, ***GUCY2D***- LEBER CONGENITAL AMAUROSIS 1, ***HADH***- 3- HYDROXYACYL-COA DEHYDROGENASE DEFICIENCY, ***HADHA***- LONG-CHAIN 3-HYDROXYACYL-COA DEHYDROGENASE DEFICIENCY; MITOCHONDRIAL TRIFUNCTIONAL PROTEIN DEFICIENCY, ***HADHB***- MITOCHONDRIAL TRIFUNCTIONAL PROTEIN DEFICIENCY, ***HAMP***- HEMOCHROMATOSIS, TYPE 2B, ***HARS2***- PERRAULT SYNDROME 2, ***HBB***- BETA THALASSEMIA; SICKLE CELL ANEMIA, ***HESX1***- SEPTOOPTIC DYSPLASIA, ***HFE2***- HEMOCHROMATOSIS, TYPE 2A, ***HGF***- DEAFNESS 39, ***HGSNAT***- MUCOPOLYSACCHARIDOSIS IIIC, ***HLCS***- HOLOCARBOXYLASE SYNTHETASE DEFICIENCY, ***HMGCL***- 3-HYDROXY-3-METHYLGLUTARYL-COA LYASE DEFICIENCY, ***HPRT1***- LESCH-NYHAN SYNDROME, ***HPS3***- HERMANSKY-PUDLAK SYNDROME 3, ***HPS4***- HERMANSKY-PUDLAK SYNDROME 4, ***HPS5***- HERMANSKY-PUDLAK SYNDROME 5, ***HPS6***- HERMANSKY-PUDLAK SYNDROME 6, ***HSD17B10***- MENTAL RETARDATION, SYNDROMIC 10, ***IDS***- MUCOPOLYSACCHARIDOSIS, TYPE II, ***IFT80***- SHORT-RIB THORACIC DYSPLASIA 2 +/- POLYDACTYLY, ***IGF1***- INSULIN-LIKE GROWTH FACTOR I DEFICIENCY, ***IKBKAP***- NEUROPATHY,HEREDITARY SENSORY AUTONOMIC, III; (FAMILIAL DYSAUTONOMIA), ***IKBKG***- INCONTINENTIA PIGMENTI; ECTODERMAL DYSPLASIA, HYPOHIDROTIC,WITH IMMUNE DEFICIENCY, ***IL2RG***- COMBINED IMMUNODEFICIENCY; SEVERE COMBINED IMMUNODEFICIENCY, ***ILDR1***- DEAFNESS 42, ***INPP5E***- JOUBERT SYNDROME 1, ***IQCB1***- SENIOR LOKEN SYNDROME 5, ***ITGB4***- EPIDERMOLYSIS BULLOSA,JUNCTIONAL, NON HERLITZ, ***IVD***- ISOVALERIC ACIDEMIA, ***JAK3***- SEVERE COMBINED IMMUNODEFICIENCY, T CELL-NEGATIVE, B CELL-POSITIVE, NK CELL-NEGATIVE, ***KCNJ1***- BARTTER SYNDROME, ANTENATAL, TYPE 2, ***KCNJ13***- LEBER CONGENITAL AMAUROSIS 16, ***KCNQ1***- JERVELL AND LANGE NIELSEN SYNDROME 1, ***KCTD7***- EPILEPSY, PROGRESSIVE MYOCLONIC, 3, +/- INTRACELLULAR INCLUSIONS, ***KIF7***- ACROCALLOSAL SYNDROME, ***L1CAM***- HYDROCEPHALUS DUE TO CONGENITAL STENOSIS OF AQUEDUCT OF SYLVIUS; MASA SYNDROME, ***LAMA2***- MUSCULAR DYSTROPHY,CONGENITAL MEROSIN DEFICIENT, 1A, ***LAMA3***- LARYNGOONYCHOCUTANEOUS SYNDROME, ***LAMP2***- DANON DISEASE (LYSOSOMAL GLYCOGEN STORAGE DISEASE WITHOUT ACID MALTASE), ***LARGE***- MUSCULAR DYSTROPHY-DYSTROGLYCANOPATHY (CONGENITAL WITH MENTAL RETARDATION), TYPE B, 6, ***LARS***- INFANTILE LIVER FAILURE SYNDROME 1, ***EVC2***- ELLIS-VAN CREVELD SYNDROME, ***LCA5***- LEBER CONGENITAL AMAUROSIS 5, ***LDLR***- HYPERCHOLESTEROLEMIA, FAMILIAL, ***LHFPL5***- DEAFNESS 67, ***LHX3***- PITUITARY HORMONE DEFICIENCY, COMBINED, 3, ***LOXHD1***- DEAFNESS 77, ***LRAT***- LEBER CONGENITAL AMAUROSIS 14, ***LRP2***- DONNAI-BARROW SYNDROME, ***LRP5***- OSTEOPOROSIS PSEUDOGLIOMA SYNDROME, ***LRTOMT***- DEAFNESS 63, ***LYST***- CHEDIAK HIGASHI SYNDROME, ***MAN2B1***- MANNOSIDOSIS, ALPHA B, LYSOSOMAL, ***MARS2***- SPASTIC ATAXIA 3, ***MARVELD2***- DEAFNESS 49, ***MCCC2***- 3-METHYLCROTONYL-COA CARBOXYLASE2 DEFICIENCY, ***MCOLN1***- MUCOLIPIDOSIS TYPE IV, ***MED12***- LUJAN FRYNS SYNDROME, ***MEFV***- FAMILIAL MEDITERRANEAN FEVER, ***MFN2***- CHARCOT-MARIE-TOOTH DISEASE, AXONAL, TYPE 2A2, ***MFSD8***- CEROID LIPOFUSCINOSIS ,NEURONAL,7, ***MGAT2***- CONGENITAL DISORDER OF GLYCOSYLATION, TYPE IIA, ***MKKS***- MCKUSICK-KAUFMAN SYNDROME; BARDET-BIEDL SYNDROME 6, ***MLC1***- MEGALENCEPHALIC LEUKOENCEPHALOPATHY WITH SUBCORTICAL CYSTS 1, ***MMAB***- METHYLMALONICACIDURIA, CBLB TYPE, ***MMACHC***- METHYLMALONIC ACIDURIA AND HOMOCYSTINURIA, CBLC TYPE, ***MOGS***- CONGENITAL DISORDER OF GLYCOSYLATION, TYPE IIB, ***MPI***- CONGENITAL DISORDER OF GLYCOSYLATION, TYPE IB, ***MPV17***- MITOCHONDRIAL DNA DEPLETION SYNDROME,HEPATOCEREBRAL, ***MPZ***- NEUROPATHY, CONGENITAL HYPOMYELINATING OR AMYELINATING, ***MRPS16***- COMBINED OXIDATIVE PHOSPHORYLATION DEFICIENCY 2, ***MTFMT***- COMBINED OXIDATIVE PHOSPHORYLATION DEFICIENCY 15, ***MTM1***- MYOPATHY, CENTRONUCLEAR, ***MTO1***- COMBINED OXIDATIVE PHOSPHORYLATION DEFICIENCY 10, ***MTPAP***- SPASTIC ATAXIA 4, ***MUT***- METHYLMALONIC ACIDURIA DUE TO METHYLMALONYL-COA MUTASE DEFICIENCY, ***MVK***- MEVALONIC ACIDURIA, ***MYO15A***- DEAFNESS 3, ***MYO6***- DEAFNESS 37, ***MYO7A***- DEAFNESS 2; USHER SYNDROME, I, ***NAGS***- N-ACETYLGLUTAMATE SYNTHASE

DEFICIENCY, ***NBN***- NIJMEGEN BREAKAGE SYNDROME, ***NDP***- NORRIE DISEASE, ***NDRG1***- CHARCOT-MARIE-TOOTH DISEASE, TYPE 4D, ***NDUFA1***- MITOCHONDRIAL COMPLEX I DEFICIENCY, ***NDUFAF5***- MITOCHONDRIAL COMPLEX I DEFICIENCY, ***NDUFS3***- LEIGH SYNDROME, ***NEB***- NEMALINE MYOPATHY 2, ***NEU1***- NEURAMINIDASE DEFICIENCY, ***NEUROG3***- DIARRHEA 4,MALABSORPTIVE, CONGENITAL, ***NHLRC1***- MYOCLONIC EPILEPSY OF LAFORA, ***NMNAT1***- LEBER CONGENITAL AMAUROSIS 9, ***NPC1***- NIEMANN-PICK DISEASE, TYPE C1, ***NPHP1***- JOUBERT SYNDROME 4; NEPHRONOPHTHISIS 1; SENIOR-LOKEN SYNDROME 1, ***NPHP4***- NEPHRONOPHTHISIS 4, ***NPHS1***- NEPHROTIC SYNDROME, TYPE 1, ***NTRK1***- CONGENITAL INSENSITIVITY TO PAINWITH ANHIDROSIS, ***NUBPL***- MITOCHONDRIAL COMPLEX I DEFICIENCY, ***NUP62***- STRIATONIGRAL DEGENERATION, INFANTILE, ***OCRL***- LOWE OCULOCEREBRO RENAL SYNDROME, ***OFD1***- 3-METHYLGLUTACONIC ACIDURIA, TYPE III, ***OTC***- ORNITHINE TRANSCARBAMYLASE DEFICIENCY, ***OTOA***- DEAFNESS 22, ***OTOF***- DEAFNESS 9, ***PAH***- PHENYLKETONURIA, ***PANK2***- NEURODEGENERATION WITH BRAIN IRON ACCUMULATION 1, ***PCDH15***- DEAFNESS 23; USHER SYNDROME, TYPE IF, ***NPHS2***- NEPHROTIC SYNDROME, TYPE 2, ***PDHX***- PYRUVATE DEHYDROGENASE E3-BINDING PROTEIN DEFICIENCY, ***PDP1***- PYRUVATE DEHYDROGENASE PHOSPHATASE DEFICIENCY, ***PLCE1***- NEPHROTIC SYNDROME, TYPE 3, ***PLG***- PLASMINOGEN DEFICIENCY, TYPE I, ***PLOD1***- EHLERS-DANLOS SYNDROME, TYPE VI, ***PLP1***- PELIZAEUS-MERZBACHER DISEASE; SPASTIC PARAPLEGIA 2, ***PMM2***- CONGENITAL DISORDER OF GLYCOSYLATION, TYPE IA, ***PMP22***- HYPERTROPHIC NEUROPATHY OF DEJERINE-SOTTAS, ***PNPO***- PYRIDOXAMINE 5-PRIME-PHOSPHATE OXIDASE DEFICIENCY, ***POU1F1***- PITUITARY HORMONE DEFICIENCY, COMBINED, 1, ***PQBP1***- RENPENNING SYNDROME 1, ***PRPS1***- ARTS SYNDROME, ***BBS9***- BARDET-BIEDL SYNDROME 9, ***PTPRQ***- DEAFNESS 84A, ***PTS***- HYPERPHENYLALANINEMIA, BH4-DEFICIENT, A, ***RAB23***- CARPENTER SYNDROME 1, ***RAB27A***- GRISCELLI SYNDROME, TYPE 2, ***RAB3GAP1***- WARBURG MICRO SYNDROME 1, ***RAB3GAP2***- MARTSOLF SYNDROME, ***RAG1***- OMENN SYNDROME; SEVERE COMBINED IMMUNODEFICIENCY, T CELL-NEGATIVE, B CELL-NEGATIVE, NK CELL-POSITIVE, ***RAG2***- OMENN SYNDROME; SEVERE COMBINED IMMUNODEFICIENCY, T CELL-NEGATIVE, B CELL-NEGATIVE, NK CELL-POSITIVE, ***RAPSN***- FETAL AKINESIA DEFORMATION SEQUENCE, ***RD3***- LEBER CONGENITAL AMAUROSIS 12, ***RDH12***- LEBER CONGENITAL AMAUROSIS 13, ***RDX***- DEAFNESS, 24, ***BLM***- BLOOM SYNDROME, ***RECQL4***- BALLER-GEROLD SYNDROME, ***RELN***- LISSENCEPHALY 2, ***RMRP***- CARTILAGE-HAIR HYPOPLASIA; ANAUXETIC DYSPLASIA, ***RPE65***- LEBER CONGENITAL AMAUROSIS 2; RETINITIS PIGMENTOSA 20, ***RPGRIP1***- LEBER CONGENITAL AMAUROSIS 6; CONE-ROD DYSTROPHY 13, ***RPS6KA3***- COFFIN-LOWRY SYNDROME, ***RS1***- RETINOSCHISIS 1, X-LINKED, JUVENILE, ***SACS***- SPASTIC ATAXIA, CHARLEVOIX-SAGUENAY TYPE, ***SBDS***- SHWACHMAN-DIAMOND SYNDROME, ***SC5D***- LATHOSTEROLOSIS, ***SCNN1A***- PSEUDOHYPOALDOSTERONISM, TYPE I, AUTOSOMAL RECESSIVE, ***SCNN1B***- PSEUDOHYPOALDOSTERONISM, TYPE I, AUTOSOMAL RECESSIVE, ***SCNN1G***- PSEUDOHYPOALDOSTERONISM, TYPE I, AUTOSOMAL RECESSIVE, ***SDHAF1***- MITOCHONDRIAL COMPLEX II DEFICIENCY, ***SEPN1***- RIGID SPINE MUSCULAR DYSTROPHY 1, ***SERAC1***- 3-METHYLGLUTACONIC ACIDURIA WITH DEAFNESS, ENCEPHALOPATHY, AND LEIGH-LIKE SYNDROME, ***SGSH***- MUCOPOLYSACCHARIDOSIS, IIIA, ***SH2D1A***- LYMPHOPROLIFERATIVE SYNDROME,1, ***SIL1***- MARINESCO-SJOGREN SYNDROME, ***SLC12A1***- BARTTER SYNDROME, ANTENATAL, TYPE 1, ***SLC12A6***- AGENESIS OF THE CORPUS CALLOSUM WITH PERIPHERAL NEUROPATHY, ***SLC16A2***- ALLAN-HERNDON-DUDLEY SYNDROME, ***SLC19A3***- THIAMINE METABOLISM DYSFUNCTION SYNDROME 2 (BIOTIN- OR THIAMINE-RESPONSIVE TYPE), ***SLC25A15***- HYPERORNITHINEMIA-HYPERAMMONEMIA-HOMOCITRULLINURIA SYNDROME, ***SLC25A4***- MITOCHONDRIAL DNA DEPLETION SYNDROME 12 (CARDIOMYOPATHIC TYPE), ***SLC26A2***- DIASTROPHIC DYSPLASIA, ***SLC35A1***- CONGENITAL DISORDER OF GLYCOSYLATION, IIF, ***SLC35C1***- CONGENITAL DISORDER O F GLYCOSYLATION, IIC, ***SLC37A4***- GLYCOGEN STORAGE DISEASE IB, ***SLC3A1***- CYSTINURIA, ***SLC6A8***- CEREBRAL CREATINE DEFICIENCY SYNDROME 1, ***SLC9A6***- MENTAL RETARDATION, SYNDROMIC, CHRISTIANSON TYPE, ***SP110***- HEPATIC VENOOCCLUSIVE DISEASE WITH IMMUNODEFICIENCY, ***SPATA7***- LEBER CONGENITAL AMAUROSIS 3, ***ST3GAL5***- AMISH INFANTILE EPILEPSY SYNDROME, ***STAR***- LIPOID CONGENITAL ADRENAL HYPERPLASIA, ***SUCLA2***- MITOCHONDRIAL DNA DEPLETION SYNDROME 5 (ENCEPHALOMYOPATHIC +/- METHYLMALONIC ACIDURIA), ***SUOX***- SULFOCYSTEINURIA, ***TBCE***- HYPOPARATHYROIDISM-RETARDATION-DYSMORPHISM SYNDROME, ***TCTN1***- JOUBERT SYNDROME 13, ***TECTA***- DEAFNESS, 21, ***TGM1***- ICHTHYOSIS, CONGENITAL, 1, ***TH***- SEGAWA SYNDROME, , ***TIMM8A***- MOHR-TRANEBJAERG SYNDROME, ***TMEM138***- JOUBERT SYNDROME 16, ***TMEM216***- JOUBERT SYNDROME 2, ***TMEM67***-

JOUBERT SYNDROME 6, ***TNFRSF11B***- PAGET DISEASE OF BONE 5, JUVENILE-ONSET, ***TNNT1***- NEMALINE MYOPATHY 5, ***TPK1***- THIAMINE METABOLISM DYSFUNCTION SYNDROME 5 (EPISODIC ENCEPHALOPATHY TYPE), ***TREX1***- AICARDI-GOUTIERES SYNDROME 1, ***TRIM37***- MULIBREY NANISM, ***TSHB***- HYPOTHYROIDISM,CONGENITAL,NONGOITROUS, 4, ***TTC21B***- NEPHRONOPHTHISIS-12; SHORT-RIB THORACIC DYSPLASIA-4 +/- POLYDACTYLY, ***TTC8***- BARDET-BIEDL SYNDROME 8, ***TTN***- MYOPATHY,EARLY ONSET,WITH FATAL CARDIOMYOPATHY, ***TULP1***- LEBER CONGENITAL AMAUROSIS 15, ***TYMP***- MITOCHONDRIAL DNA DEPLETION SYNDROME 1 (MNGIE TYPE), ***UGT1A1***- CRIGLER-NAJJAR SYNDROME, TYPE I, ***UQCRQ***- MITOCHONDRIAL COMPLEX III DEFICIENCY, NUCLEAR TYPE 4, ***UROS***- PORPHYRIA,CONGENITAL ERYTHROPOIETIC, ***USH1C***- USHER SYNDROME, IC, ***USH1G***- USHER SYNDROME, TYPE IG, ***USH2A***- USHER SYNDROME, TYPE IIA, ***VDR***- VITAMIN D-DEPENDENT RICKETS, TYPE 2A, ***VLDLR***- CEREBELLAR ATAXIA, MENTAL RETARDATION, AND DYSEQUILIBRIUM SYNDROME 1, ***VPS13B***- COHEN SYNDROME, ***WDR19***- NEPHRONOPHTHISIS 13; SENIOR-LOKEN SYNDROME 8,***WFS1***- WOLFRAM SYNDROME 1, ***XPA***- XERODERMA PIGMENTOSUM, COMPLEMENTATION GROUP A, ***YARS2***- MYOPATHY, LACTIC ACIDOSIS, AND SIDEROBLASTIC ANEMIA 2, ***ZIC3***- VACTERL ASSOCIATION, +/- HYDROCEPHALUS; HETEROTAXY,VISCERAL, 1

CATEGORY: MILD

ABCA4- CONE ROD DYSTROPHY 3; STARGARDT DISEASE, ***AFF2***- MENTAL RETARDATION, ASSOCIATED WITH FRAGILE SITE FRAXE, ***ALAS2***- ANEMIA, SIDEROBLASTIC, ***ALDOB***- FRUCTOSE INTOLERANCE, HEREDITARY, ***AR***- ANDROGEN INSENSITIVITY SYNDROME; INFERTILE MALE SYNDROME, ***BEST1***- BESTROPHINOPATHY; RETINITIS PIGMENTOSA 50, ***BSND***- BARTTER SYNDROME, TYPE 4A, ***C2ORF71***- RETINITIS PIGMENTOSA 54, ***C8ORF37***- CONE-ROD DYSTROPHY 16, ***CERKL***- RETINITIS PIGMENTOSA 26, ***CIB2***- DEAFNESS 48, ***CNGA1***- RETINITIS PIGMENTOSA 49, ***CNGA3***- ACHROMATOPSIA 2, ***CNGB1***- RETINITIS PIGMENTOSA 45, ***CNGB3***- ACHROMATOPSIA, ***COL11A2***- DEAFNESS 53; OTOSPONDYLOMEGAEPIPHYSEAL DYSPLASIA, ***CRB1***- RETINITIS PIGMENTOSA 12, ***CYP27A1***- CEREBROTENDINOUS XANTHOMATOSIS, ***CYP27B1***- VITAMIN D HYDROXYLATION-DEFICIENT RICKETS, TYPE 1A, ***DHDDS***- RETINITIS PIGMENTOSA 59, ***EDA***- ECTODERMAL DYSPLASIA, HYPOHIDROTIC, ***EDNRB***- ABCD SYNDROME, ***EYS***- RETINITIS PIGMENTOSA 25, ***F11***- FACTOR XI DEFICIENCY, ***FAM161A***- RETINITIS PIGMENTOSA 28, ***FGD1***- AARSKOG-SCOTT SYNDROME, ***G6PD***- ANEMIA, NONSPHEROCYTIC HEMOLYTIC, DUE TO G6PD DEFICIENCY, ***GJB1***- CHARCOT-MARIE-TOOTH DISEASE, 1, ***GJB2***- DEAFNESS 1A, ***GNAT2***- ACHROMATOPSIA 4, ***GP1BA***- BERNARD-SOULIER SYNDROME TYPE A1, ***GP9***- BERNARD-SOULIER SYNDROME TYPE C, ***GPC3***- SIMPSON-GOLABI-BEHMEL SYNDROME, TYPE 1, ***GPR143***- ALBINISM, OCULAR, TYPE I, ***GYS2***- GLYCOGEN STORAGE DISEASE 0, LIVER, ***HPS1***- HERMANSKY-PUDLAK SYNDROME 1, ***IDH3B***- RETINITIS PIGMENTOSA 46, ***IMPG2***- RETINITIS PIGMENTOSA 56, ***ISCU***- MYOPATHY WITH LACTIC ACIDOSIS, HEREDITARY, ***KAL1***- HYPOGONADOTROPIC HYPOGONADISM 1 +/- ANOSMIA, ***LDLRAP1***- HYPERCHOLESTEROLEMIA, ***MERTK***- RETINITIS PIGMENTOSA 38, ***MTTP***- ABETALIPOPROTEINEMIA, ***NR2E3***- ENHANCED S-CONE SYNDROME; RETINITIS PIGMENTOSA 37, ***NRL***- RETINAL DEGENERATION, CLUMPED PIGMENT TYPE, INCLUDED, ***OCA2***- ALBINISM, OCULOCUTANEOUS, TYPE II, ***PDE6A***- RETINITIS PIGMENTOSA 43, ***PDE6B***- RETINITIS PIGMENTOSA 40, ***PDE6C***- CONE DYSTROPHY 4, ***PDE6G***- RETINITIS PIGMENTOSA 57, ***PDE6H***- RETINAL CONE DYSTROPHY 3A, ***PKLR***- PYRUVATE KINASE DEFICIENCY OF RED CELLS, ***PLEKHG5***- SPINAL MUSCULAR ATROPHY, DISTAL, 4, ***POU3F4***- DEAFNESS 2, ***PRCD***- RETINITIS PIGMENTOSA 36, ***PROM1***- RETINITIS PIGMENTOSA 41, ***PRX***- HYPERTROPHIC NEUROPATHY OF DEJERINE-SOTTAS, ***PUS1***- MYOPATHY, LACTIC ACIDOSIS, AND SIDEROBLASTIC ANEMIA 1, ***RGR***- RETINITIS PIGMENTOSA 44, ***RLBP1***- BOTHNIA RETINAL DYSTROPHY, ***RP1***- RETINITIS PIGMENTOSA 1, ***RP2***- RETINITIS PIGMENTOSA 2, ***RPGR***- CONE-ROD DYSTROPHY; MACULAR DEGENERATION, ATROPHIC; RETINITIS PIGMENTOSA, AND SINORESPIRATORY INFECTIONS, +/- DEAFNESS, ***SAG***- OGUCHI DISEASE-1; RETINITIS PIGMENTOSA 47, ***SLC26A4***- DEAFNESS, 4, WITH ENLARGED VESTIBULAR AQUEDUCT; PENDRED SYNDROME, ***SLC26A5***- DEAFNESS, AUTOSOMAL RECESSIVE 61, ***SLC45A2***- ALBINISM, OCULOCUTANEOUS, TYPE IV, ***SLC4A11***- CORNEAL ENDOTHELIAL DYSTROPHY 2; CORNEAL DYSTROPHY AND PERCEPTIVE DEAFNESS, ***SLC7A9***- CYSTINURIA, ***SMPX***- DEAFNESS 4, ***STRC***- DEAFNESS 16, ***STS***- ICHTHYOSIS, ***TMC1***- DEAFNESS 7, ***TMEM126A***- OPTIC ATROPHY 7 +/- AUDITORY NEUROPATHY, ***TMIE***- DEAFNESS 6, ***TMPRSS3***- DEAFNESS 8, ***TPRN***- DEAFNESS 79, ***TRAPPC2***- SPONDYLOEPIPHYSEAL DYSPLASIA TARDA, ***TRIM32***- LIMB-GIRDLE MUSCULAR

DYSTROPHY 2H, ***TRIOBP***- DEAFNESS 28, ***TRMU***- LIVER FAILURE, INFANTILE, TRANSIENT, ***TTPA***- VITAMIN E, FAMILIAL ISOLATED DEFICIENCY OF, ***TULP1***- RETINITIS PIGMENTOSA 14, ***TYR***- ALBINISM, OCULOCUTANEOUS, TYPE IA; ALBINISM, OCULOCUTANEOUS, TYPE IB, ***TYRP1***- ALBINISM, OCULOCUTANEOUS, TYPE III, ***UGT1A1***- GILBERT SYNDROME, ***WNT10A***- ODONTOONYCHODERMAL DYSPLASIA, ***WNT7A***- FIBULAR APLASIA OR HYPOPLASIA, FEMORAL BOWING AND POLY-, SYN-, AND OLIGODACTYLY, ***ZNF469***- BRITTLE CORNEA SYNDROME 1

CATEGORY: LATE ONSET

AMPD1- MYOADENYLATE DEAMINASE DEFICIENCY, ***CP***- ACERULOPLASMINEMIA, ***GNE***- INCLUSION BODY MYOPATHY 2, ***HFE***- HEMOCHROMATOSIS, TYPE 1, ***HGD***- ALKAPTONURIA, ***MAK***- RETINITIS PIGMENTOSA 62, ***MUTYH***- FAMILIAL ADENOMATOUS POLYPOSIS, 2, ***MYO3A***- DEAFNESS 30, ***SERPINA1***- ALPHA-1-ANTITRYPSIN DEFICIENCY, ***SPG7***- SPASTIC PARAPLEGIA 7, ***VPS13A***- CHOREOACANTHOCYTOSIS

CATEGORY: UNPREDICTABLE

ACADS- SHORT-CHAIN ACYL-COA DEHYDROGENASE DEFICIENCY, ***ACADSB***- 2-METHYLBUTYRYL-COA DEHYDROGENASE DEFICIENCY, ***ADCK3***- COENZYME Q10 DEFICIENCY, PRIMARY, 4, ***ANTXR2***- HYALINE FIBROMATOSIS SYNDROME, ***AUH***- 3-METHYLGLUTACONIC ACIDURIA, TYPE I, ***COQ2***- COENZYME Q10 DEFICIENCY, ***CPT2***- CARNITINE PALMITOYLTRANSFERASE DEFICIENCY II, ***DARS2***- LEUKOENCEPHALOPATHY WITH BRAINSTEM AND SPINAL CORD INVOLVEMENT AND LACTATE ELEVATION, ***F5***- COAGULATION FACTOR V, ***FANCC***- FANCONI ANEMIA COMPLEMENTATION GROUP C, ***FGA***- AFIBRINOGENEMIA, CONGENITAL, ***FGB***- AFIBRINOGENEMIA, CONGENITAL, ***FGD4***- CHARCOT-MARIE-TOOTH-DISEASE,4H, ***FGG***- AFIBRINOGENEMIA, CONGENITAL, ***GBA***- GAUCHER DISEASE, TYPE I; GAUCHER DISEASE, TYPE II; GAUCHER DISEASE, TYPE III; GAUCHER DISEASE, TYPE IIIC, ***MED12***- OPITZ-KAVEGGIA SYNDROME, ***MPZ***- HYPERTROPHIC NEUROPATHY OF DEJERINE-SOTTAS, ***MTHFR***- HOMOCYSTINURIA DUE TO DEFICIENCY OF N(5,10)-METHYLENETETRAHYDROFOLATE REDUCTASE ACTIVITY, ***MT-ND5***- LEBER HEREDITARY OPTIC NEUROPATHY; MITOCHONDRIAL MYOPATHY, ENCEPHALOPATHY, LACTIC ACIDOSIS, AND STROKE-LIKE EPISODESLEIGH SYNDROME, ***MT-TF***- MITOCHONDRIAL MYOPATHY, ENCEPHALOPATHY, LACTIC ACIDOSIS, AND STROKE-LIKE EPISODES; MYOCLONIC EPILEPSY ASSOCIATED WITH RAGGED-RED FIBERS, ***MT-TH***- MYOCLONIC EPILEPSY ASSOCIATED WITH RAGGED-RED FIBERS LEBER HEREDITARY OPTIC NEUROPATHY; MITOCHONDRIAL MYOPATHY, ENCEPHALOPATHY, LACTIC ACIDOSIS, AND STROKE-LIKE EPISODES, ***MT-TK***- MYOCLONIC EPILEPSY ASSOCIATED WITH RAGGED-RED FIBERS, ***MT-TL1***- LEBER HEREDITARY OPTIC NEUROPATHY; MYOCLONIC EPILEPSY ASSOCIATED WITH RAGGED-RED FIBERS MITOCHONDRIAL MYOPATHY, ENCEPHALOPATHY, LACTIC ACIDOSIS, AND STROKE-LIKE EPISODES, ***MT-TS1***- MYOCLONIC EPILEPSY ASSOCIATED WITH RAGGED-RED FIBERS MITOCHONDRIAL MYOPATHY, ENCEPHALOPATHY, LACTIC ACIDOSIS, AND STROKE-LIKE EPISODES; DEAFNESS, NONSYNDROMIC SENSORINEURAL, MITOCHONDRIAL, ***MT-TS2***- MYOCLONIC EPILEPSY ASSOCIATED WITH RAGGED-RED FIBERS MITOCHONDRIAL MYOPATHY, ENCEPHALOPATHY, LACTIC ACIDOSIS, AND STROKE-LIKE EPISODES, ***MVK***- HYPER-IGD SYNDROME, ***NAGA***- SCHINDLER DISEASE, TYPE I, ***NR0B1***- 46,XY SEX REVERSAL 2, ***POLG***- MITOCHONDRIAL DNA DEPLETION SYNDROME 4B; SENSORY ATAXIC NEUROPATHY, DYSARTHRIA, AND OPHTHALMOPARESIS; PROGRESSIVE EXTERNAL OPHTHALMOPLEGIA WITH MITOCHONDRIAL DNA DELETIONS 1, ***PROC***- THROMBOPHILIA DUE TO PROTEIN C DEFICIENCY, ***PYGM***- GLYCOGEN STORAGE DISEASE V, ***SGCA***- MUSCULAR DYSTROPHY, LIMB-GIRDLE, TYPE 2D, ***SGCB***- MUSCULAR DYSTROPHY, LIMB-GIRDLE, TYPE 2E, ***SLC22A5***- CARNITINE DEFICIENCY, SYSTEMIC PRIMARY, ***SLC25A13***- CITRULLINEMIA, TYPE II, NEONATAL-ONSET, ***SLC34A2***- PULMONARY ALVEOLAR MICROLITHIASIS, ***TFR2***- HEMOCHROMATOSIS, TYPE 3, ***TTC19***- MITOCHONDRIAL COMPLEX III DEFICIENCY, NUCLEAR TYPE 2

Incidental Findings Results: No known pathogenic variants detected in genes causative of genetic conditions that are medically actionable (incidental findings).

Interpretation:

This individual requested to learn about findings of genetic conditions that are medically actionable (incidental findings; please see attached list). Our analysis did not identify any medically actionable findings in this individual. However, it is important to understand that genome sequencing is a screening test. This individual could carry a variant not detected by this test (see test limitations). In addition, only known pathogenic or likely pathogenic variants are reported.

Recommendations:

Genetic counseling is recommended if the patient has unresolved questions.

ACTIONABLE GENES

ACTA2 : Aortic aneurysm, familial thoracic ; *ACTC1*: Cardiomyopathy, dilated; Cardiomyopathy, familial hypertrophic; Left ventricular noncompaction ; *ACVRL1* : Telangiectasia, hereditary hemorrhagic ; *APC* : Familial adenomatous polyposis ; *APOB*: Familial hypercholesterolemia *few pathogenic variants; *BMPR1A*: Juvenile polyposis syndrome; *BRCA1* : Hereditary breast and ovarian cancer ; *BRCA2* : Hereditary breast and ovarian cancer susceptibility; *CACNA1C*: *SQTS-4*; *CACNA1S*: Malignant hyperthermia susceptibility ; *CACNB2*: *SQTS-5*; *CDC73*: Hyperparathyroidism-jaw tumor syndrome; *CDH1* : Hereditary diffuse gastric cancer ; *CDKN2A*: Melanoma and pancreatic cancer (mild/moderate genetic risk gene) ; *CNBPx*: Myotonic dystrophy 2; *COL3A1*: Ehlers-Danlos syndrome, vascular; *COL5A1*: Ehlers-Danlos syndrome, classic ; *COL5A2*: Ehlers-Danlos syndrome, classic; *DMPK*^{X}: Myotonic dystrophy 1; *DSC2*: Arrhythmogenic right ventricular dysplasia ; *DSG2*: Arrhythmogenic right ventricular dysplasia; Cardiomyopathy, dilated; *DSP*: Arrhythmogenic right ventricular dysplasia; *ENG*: Hereditary Hemorrhagic Telangiectasia; *EPCAM*: Hereditary nonpolyposis colorectal cancer/Lynch syndrome; *FBN1* : Marfan syndrome ; *FH* : Leiomyomatosis and renal cell cancer ; *FLCN*: Birt- Hogg-Dube syndrome ; *GCH1* : Dystonia, DOPA-responsive, with or without hyperphenylalaninemia ; *GREM1*: Hereditary Mixed Polyposis; *HMBS*: Porphyria, acute intermittent; *KCNE1* : LQTS-5; *KCNE2* : LQTS-6; *KCNH2* : LQTS-2, SQTS-1; *KCNQ1* : LQTS-1, SQTS-2; *KIT*: Gastrointestinal stromal tumor; *LDLR*: Hypercholesterolemia, familial ; *LMNA*: Cardiomyopathy; *MAX*: Susceptibility to pheochromocytoma; *MEN1* : Multiple endocrine neoplasia, type 1; *MET*: Renal cell carcinoma, papillary, familial ; *MLH1* : Hereditary nonpolyposis colorectal cancer/Lynch syndrome; *MSH2* : Hereditary nonpolyposis colorectal cancer/Lynch syndrome; *MSH6* : Hereditary nonpolyposis colorectal cancer/Lynch syndrome; *MUTYH* : MYH Associated polyposis ; *MYBPC3*: Cardiomyopathy, dilated; Cardiomyopathy, familial hypertrophic; *MYH11* : Aortic aneurysm, familial thoracic ; *MYH7*: Cardiomyopathy, dilated; Cardiomyopathy, familial hypertrophic; Left ventricular noncompaction; *MYL2*: Cardiomyopathy, familial hypertrophic; *MYL3*: Cardiomyopathy, familial hypertrophic; *MYLK*: Aortic aneurysm, familial thoracic; *NF2* : Neurofibromatosis, type 2 ; *PALB2*: Breast cancer, susceptibility; Pancreatic cancer, susceptibility; *PCSK9*: Familial hypercholesterolemia; *PDGFRA*: Gastrointestinal stromal tumor; *PKP2*: Arrhythmogenic right ventricular dysplasia ; *PLN*: Cardiomyopathy, dilated; Cardiomyopathy, familial hypertrophic; *PMS2* : Hereditary nonpolyposis colorectal cancer/Lynch syndrome; *POLD1*: Colorectal adenomas and carcinomas *only exonuclease domain; *POLE*: Colorectal adenomas and carcinomas *only exonuclease domain; *PRKAG2* : Wolff-Parkinson-White syndrome; Cardiomyopathy, hypertrophic 6 ; *PRKAR1A*: Carney complex, type 1 ; *PRKG1*: Familial thoracic aortic aneurysm *1 variant only c.530C>A, p.Arg177Gln; *PROC*: Thrombophilia due to protein C deficiency; *PROS1*: Thrombophilia due to protein S deficiency; *PRRT2*: Paroxysmal kinesigenic dyskinesia ; *PTCH1*: Basal cell nevus syndrome ; *PTEN* : Cowden syndrome; *RBM20*: Cardiomyopathy, dilated; *RET* : Multiple endocrine neoplasia Type 2 ; *RYR1*: Malignant hyperthermia susceptibility 1; *RYR2*: Arrhythmogenic right ventricular dysplasia; *SCG5*: Hereditary Mixed Polyposis; *SCN5A* : LQTS-3; BRGDA 1; *SDHAF2* : Hereditary paragangliomas and pheochromocytomas ; *SDHB* : Hereditary paragangliomas and pheochromocytomas ;*SDHC* : Hereditary paragangliomas and pheochromocytomas ; *SDHD* : Hereditary paragangliomas and pheochromocytomas ;

SERPINC1: Thrombophilia due to antithrombin III deficiency; *SGCD*: Cardiomyopathy, dilated; *SMAD3*: Loeys-Dietz syndrome 1C ; *SMAD4* : Juvenile polyposis syndrome; *STK11* : Peutz-Jeghers syndrome ; *TGFB2*: Loeys-Dietz syndrome, type 4; *TGFB3*: Arrhythmogenic right ventricular dysplasia 1; *TGFBR1* : Loeys-Dietz syndrome, type 1A and type 2A; *TGFBR2* : Hereditary nonpolyposis colorectal cancer/Lynch syndrome / Loeys-Dietz syndrome ; *TMEM127*: Susceptibility to pheochromocytoma; *TMEM43*: Arrhythmogenic right ventricular dysplasia 5; *TNNI3*: Cardiomyopathy, dilated; Cardiomyopathy, familial hypertrophic; *TNNT2*: Cardiomyopathy, dilated; Cardiomyopathy, familial hypertrophic; *TP53* : Li-Fraumeni syndrome ; *TPM1*: Cardiomyopathy, dilated; Cardiomyopathy, familial hypertrophic; *TSC1*: Tuberous sclerosis complex; *TSC2*: Tuberous sclerosis complex; *VHL* : von Hippel-Lindau syndrome

AUTOSOMAL RECESSIVE *(Homozygotes/compound heterozygotes)*

ATP7B: Wilson disease ; *BCHE*: Pseudocholinesterase deficiency (homozygotes for null alleles only); *BLM*: Bloom syndrome; *CASQ2*: Ventricular tachycardia, catecholaminergic polymorphic; *CFTR*: Cystic fibrosis; *CPT2*: CPT deficiency, hepatic, type II; *F5*: Factor V deficiency; *GAA*: Glycogen storage disease II; *HAMP*: Hemochromatosis, type 2B; *HFE*: Hemochromatosis *C282Y only (mild/moderate genetic risk gene); *HFE2*: Hemochromatosis, type 2A; *IDUA*: Mucopolysaccharidosis; *DLRAP1*: Hypercholesterolemia, familial; *PAH*: Phenylketonuria; *PCBD1*: Hyperphenylalaninemia, BH4-deficient, D; *PTS*: Hyperphenylalaninemia, BH4-deficient, A; *QDPR*: Hyperphenylalaninemia, BH4-deficient, C; *SERPINA1*: Emphysema due to AAT deficiency; *SLC25A13*:Citrullinemia, adult-onset type II; *SLC37A* : Glycogen storage disease Ib; Glycogen storage disease Ic; *SLC7A9*: Cystinuria; *SLC3A1*: Cystinuria

X-LINKED

DMD: Becker muscular dystrophy; Cardiomyopathy, dilated; Duchenne muscular dystrophy; *EMD*: Emery- Dreifuss muscular dystrophy 1; *GLA*: Fabry disease; *OTC*: Ornithine transcarbamylase deficiency

Figure S1

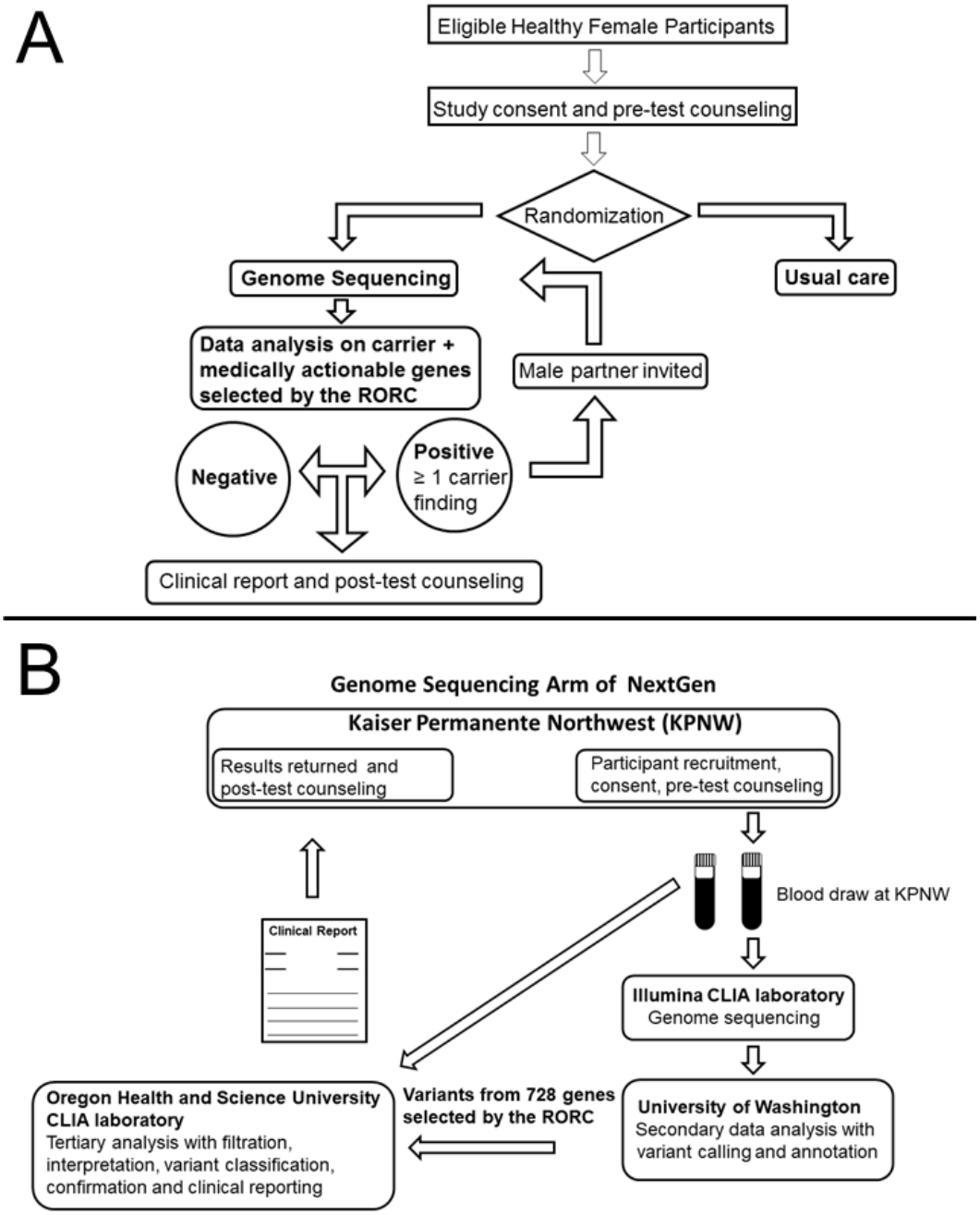

Figure S1: NextGen Study Design

A) A schematic representation of the sequential model for carrier screening in the NextGen study design. Participant surveys were conducted at the beginning of the study, upon receiving results, as well as a final survey at the end of the study for both arms, the Usual Care arm and the GS arm. B) Collaborators in the NextGen study. Further details are in the Methods section in the main text. RORC – Return of Results Committee

Table S1

Variant type	Percentage (%) (n= 195)
missense	48
nonsense	19
frameshift	18
Splice-error	11
Multi-exon deletion	2
Synonymous/splice-error	1
Whole gene deletion	0.5
In-frame deletion	0.5

Table S1: Frequency of the various types of variants reported in the study.
The percentage is based on 195 'distinct' variants (any repeated variant was not included) and includes both known and novel variants. The distribution of variant type is dependent on the pathogenic mechanism of disease for the genes-disorder categories as well as the sensitivity and specificity of the sequencing platform.