Mitochondrial Disorders Panel (mtDNA Sequencing, Nuclear Genes Sequencing and Deletion/Duplication)

Indications for Ordering

- Complex neurological features or a single neurological symptom and other system involvement
- Clinical symptoms characteristic of a specific mitochondrial disorder
- Progressive multisystem disorder of unknown etiology
- Presymptomatic testing for at-risk family members

Contraindications for Ordering

Disorders commonly caused by large deletions in mitochondrial DNA (mtDNA)

- Chronic progressive external ophthalmoplegia (CPEO)
- Kearns-Sayre syndrome (KSS)
- Pearson syndrome

Test Description

- mtDNA genome
  - Amplification by long-range polymerase chain reaction (LRPCR) followed by massively parallel sequencing
  - Reference sequence NC_012920 is used for data analysis
- Nuclear genes
  - Targeted capture of all coding exons and intron/exon junctions followed by massively parallel sequencing
  - Custom-designed comparative genomic hybridization (CGH) array to detect large deletions/duplications
    - CGH does not include *LARS2* and *NDUFA2*
- Human genome build 19 (hg19) is used for data analysis
- Sequence variants reported are confirmed by Sanger sequencing

Tests to Consider

Primary test

Mitochondrial Disorders Panel (mtDNA Sequencing, Nuclear Genes Sequencing and Deletion/Duplication) 2006054

Preferred test to confirm a suspected diagnosis of a mitochondrial disorder caused by a mtDNA genome sequence variant or variant(s) in related nuclear genes

Related test

Mitochondrial Disorders (mtDNA) Sequencing 2006065

Assess for sequence variants in mtDNA that cause mitochondrial disorders

Disease Overview

Incidence – 1/5,000 in U.S.

Symptoms

- Mitochondrial disorders are clinically and genetically heterogeneous
- Tissues most affected by mitochondrial disease
  - Are dependent on aerobic metabolism
  - Have a high energy requirement
- Some mitochondrial disorders affect single organs, such as the eye or ear, while others affect multiple systems
- Symptoms may present at any age, and phenotype may change with age
  - Poor growth
  - Neurological problems
    - Seizures
    - Encephalopathy
    - Ataxia
    - Spasticity
    - Stroke-like episodes
  - Loss of vision or hearing
  - Liver, kidney, heart disease
  - Myopathy and muscle weakness
- Severity of disease resulting from variants in mtDNA may be influenced by the presence of heteroplasmy (ratio of mutated to normal mitochondria within a cell, tissue, or individual)
- Common mitochondrial syndromes – see table 1

Genes – see tables 2 and 3 for genes tested

Inheritance

Variable, dependent on the gene(s) involved – see table 4

- Nuclear genes – autosomal recessive, autosomal dominant, or X-linked recessive
- Mitochondrial genome – maternal

Penetrance

Variable – dependent on the gene(s) involved and the level of heteroplasmy

Test Interpretation

Clinical sensitivity – unknown

Results

- Positive
  - One or more pathogenic variants detected
    - mtDNA variants will be reported as
      - Homoplasmic
        - ≥99% of mtDNA sequences are identical
      - Heteroplasmic
        - <99% of mtDNA sequences are identical
        - Percentage of heteroplasmy is not reported
- Negative
  - No pathogenic variants detected
- Inconclusive
  - One or more variants of uncertain clinical significance detected

Limitations

- Not detected
  - Large deletions/duplications within the mtDNA genome
  - Variants in genes not analyzed
  - Regulatory region and deep intronic variants
  - Large deletions/duplications in *LARS2* or *NDUFA2*
- mtDNA variants present at <10% heteroplasmy may not be detected
- Sequencing may detect variants of unknown clinical significance
- Diagnostic errors can occur due to rare sequence variations
- Presence of a highly homologous pseudogene may interfere with variant detection in *WFS1*
- Variants in the following exons are not detected:
  - *ETFB* (NM_001985): exon 1
  - *FXN* (NM_001161706): exon 5
  - *NDUFA11* (NM_001193375): exon 4
  - *TSFM* (NM_001172697): exon 6
- Not reported
  - Variants in the mitochondrial D-loop
  - Mosaic variants in nuclear genes
  - Percentage of heteroplasmy

Table 1: Common Mitochondrial Syndromes

Disorder	Major Clinical Features	Inheritance	Commonly Associated Genes/Variants
Chronic progressive external ophthalmoplegia (CPEO)	External ophthalmoplegia Bilateral ptosis Mild proximal myopathy	Sporadic	mtDNA large deletions confined to skeletal muscle in ~50% of cases
		Maternal	Various mtDNA point variants
		Autosomal dominant/recessive	eg, *C10orf2, OPA1*, *POLG, POLG2, RRMB2, SLC25A4, SPG7, TYMP*
Kearns-Sayre syndrome (KSS)	PEO onset <20 years of age Pigmentary retinopathy CSF protein >1g/L Cerebellar ataxia Heart block	Sporadic (infrequently maternally transmitted)	Large mtDNA large deletions in ~90% of cases m.8470_1344del4977 is most frequent
Leber hereditary optic neuropathy (LHON)	Subacute painless bilateral visual failure Median age of onset 24 years Males:females, 4:1	Maternal	90% of cases due to one of three common mtDNA variants *MT-ND4* m.11778G>A *MT-ND6* m.14484T>C *MT-ND1* m.3460G>A Variants in other mtDNA genes are rare causes of LHON
Leigh syndrome (LS)	Progressive neurological disease with motor and intellectual developmental delay Cerebellar and brain stem signs Infantile onset	Maternal	mtDNA large deletions causative for <5% of LS *MT-ATP6* (10% of cases) Other mtDNA genes (10-20% of cases)
		Autosomal recessive or X-linked recessive	Majority of cases due to nuclear gene variants (numerous genes implicated)

Table 1: Common Mitochondrial Syndromes			
Disorder	**Major Clinical Features**	**Inheritance**	**Commonly Associated Genes/Variants**
Mitochondrial encephalomyopathy with lactic acidosis and stroke-like episodes (MELAS)	Stroke-like episodes <40 years of age Encephalopathy with seizures and/or dementia Mitochondrial myopathy, evidenced by lactic acidosis and/or ragged-red fibers	Maternal	*MT-TL1* (accounts for majority of cases) m.3243A>G m.3271T>C m.3252A>G *MT-ND5* m.13513G>A Variants in other mtDNA genes are rare
Myoclonic epilepsy with ragged-red fibers (MERRF)	Myoclonus Seizures Cerebellar ataxia Myopathy	Maternal	*MT-TK* (accounts for ~90% of cases) m.8344A>G m.8356T>C m.8363G>A m.8361G>A Causative variants in other mtDNA genes, including *MT-TP* and *MT-TF*, account for <5% of cases
Neurogenic weakness with ataxia and retinitis pigmentosa (NARP)	Late-childhood or adult-onset peripheral neuropathy Ataxia Pigmentary retinopathy	Maternal	*MT-ATP6* (estimated to account for >50% of cases) m.8993T>G m.8993T>C
Pearson syndrome	Sideroblastic anemia of childhood Pancytopenia Exocrine pancreatic failure	Sporadic (infrequently maternally transmitted)	mtDNA large deletions

Table 2: Mitochondrial DNA (mtDNA) Genes[a] Tested			
Gene Symbol	**Gene Description**	**OMIM #**	**Inheritance**
MT-ATP6	Mitochondrially encoded ATP synthase 6 (overlaps *MT-ATP8* gene)	516060	Maternal
MT-ATP8	Mitochondrially encoded ATP synthase 8 (overlaps *MT-ATP6* gene)	516070	Maternal
MT-CO1	Mitochondrially encoded cytochrome c oxidase I	516030	Maternal
MT-CO2	Mitochondrially encoded cytochrome c oxidase II	516040	Maternal
MT-CO3	Mitochondrially encoded cytochrome c oxidase III	516050	Maternal
MT-CYB	Mitochondrially encoded cytochrome b	516020	Maternal
MT-ND1	Mitochondrially encoded NADH dehydrogenase 1	516000	Maternal
MT-ND2	Mitochondrially encoded NADH dehydrogenase 2	516001	Maternal
MT-ND3	Mitochondrially encoded NADH dehydrogenase 3	516002	Maternal
MT-ND4	Mitochondrially encoded NADH dehydrogenase 4	516003	Maternal
MT-ND4L	Mitochondrially encoded NADH dehydrogenase 4L	516004	Maternal
MT-ND5	Mitochondrially encoded NADH dehydrogenase 5	516005	Maternal
MT-ND6	Mitochondrially encoded NADH dehydrogenase 6	516006	Maternal
MT-RNR1	Mitochondrially encoded 12S RNA	561000	Maternal
MT-RNR2	Mitochondrially encoded 16S RNA	561010	Maternal
MT-TA	Mitochondrially encoded tRNA alanine	590000	Maternal
MT-TC	Mitochondrially encoded tRNA cysteine	590020	Maternal
MT-TD	Mitochondrially encoded tRNA aspartic acid	590015	Maternal
MT-TE	Mitochondrially encoded tRNA glutamic acid	590025	Maternal
MT-TF	Mitochondrially encoded tRNA phenylalanine	590070	Maternal
MT-TG	Mitochondrially encoded tRNA glycine	590035	Maternal
MT-TH	Mitochondrially encoded tRNA histidine	590040	Maternal
MT-TI	Mitochondrially encoded tRNA isoleucine	590045	Maternal
MT-TK	Mitochondrially encoded tRNA lysine	590060	Maternal
MT-TL1	Mitochondrially encoded tRNA leucine 1 (UUA/G)	590050	Maternal
MT-TL2	Mitochondrially encoded tRNA leucine 2 (CUN)	590055	Maternal

Table 2: Mitochondrial DNA (mtDNA) Genes[a] Tested			
Gene Symbol	**Gene Description**	**OMIM #**	**Inheritance**
MT-TM	Mitochondrially encoded tRNA methionine	590065	Maternal
MT-TN	Mitochondrially encoded tRNA asparagine	590010	Maternal
MT-TP	Mitochondrially encoded tRNA proline	590075	Maternal
MT-TQ	Mitochondrially encoded tRNA glutamine	590030	Maternal
MT-TR	Mitochondrially encoded tRNA arginine	590005	Maternal
MT-TS1	Mitochondrially encoded tRNA serine 1 (UCN)	590080	Maternal
MT-TS2	Mitochondrially encoded tRNA serine 2 (AGU/C)	590085	Maternal
MT-TT	Mitochondrially encoded tRNA threonine	590090	Maternal
MT-TV	Mitochondrially encoded tRNA valine	590105	Maternal
MT-TW	Mitochondrially encoded tRNA tryptophan	590095	Maternal
MT-TY	Mitochondrially encoded tRNA tyrosine	590100	Maternal
[a]All mitochondrial genes are reference sequence NC_012920			

Table 3: Nuclear Genes Tested					
Gene Symbol	**Gene Description**	**NM #**	**OMIM #**	**Inh.**	**Commonly Associated Disorder(s)**
ABCB7	ATP-binding cassette, sub-family B (MDR/TAP), member 7	004299	300135	XL	Sideroblastic anemia and ataxia
ACAD9	acyl-Coenzyme A dehydrogenase family, member 9	014049	611103	AR	Complex 1 deficiency, ACAD9 deficiency
ACADL	acyl-CoA dehydrogenase, long chain	001608	609576	Unknown	LCAD deficiency
ACADM	acyl-CoA dehydrogenase, medium chain	000016	607008	AR	MCAD deficiency
ACADS	acyl-CoA dehydrogenase, short chain	000017	606885	AR	SCAD deficiency
ACADVL	Very long chain acyl-CoA dehydrogenase	000018	609575	AR	VLCAD deficiency
ACAT1	Acetoacetyl 1-CoA thiolase	000019	607809	AR	Acetoacetyl-CoA-thiolase deficiency
ADCK3	aarF domain containing kinase 3	020247	606980	AR	Ubiquinone deficiency with cerebellar ataxia
APTX	Aprataxin	175073	606350	AR	Ataxia-ocular apraxia 1
ASS1	Argininosuccinate synthetase	000050	603470	AR	Citrullinemia type I
ATPAF2	ATP synthase mitochondrial F1 complex assembly factor 2	145691	608918	AR	Complex V deficiency
BCKDHA	Branched chain keto acid dehydrogenase E1, alpha polypeptide	000709	608348	AR	Maple syrup urine disease type 1A
BCKDHB	Branched chain keto acid dehydrogenase E1, beta polypeptide	183050	248611	AR	Maple syrup urine disease type 1B
BCS1L	BCS1 (yeast homologue)-like	004328	603647	AR	Complex 3 deficiency
C10orf2	Chromosome 10 open reading frame 2	021830	606075	AD/AR	Infantile-onset spinocerebellar ataxia, progressive external ophthalmoplegia
COQ2	Coenzyme Q2 homologue, prenyltransferase (yeast)	015697	609825	AR	Primary coenzyme Q10 deficiency 1
COQ9	Coenzyme Q9 homolog (S. cerevisiae)	020312	612837	AR	Primary coenzyme Q10 deficiency
COX10	COX10 (yeast) homologue, cytochrome C oxidase assembly protein (haem A: farnesyltransferase)	001303	602125	AR	Cytochrome c oxidase deficiency
COX15	COX15 homologue, cytochrome c oxidase assembly protein (yeast)	078470	603646	AR	Cytochrome c oxidase deficiency 2, Leigh syndrome
COX4I2	Cytochrome c oxidase subunit IV isoform 2 (lung)	032609	607976	AR	Exocrine pancreatic insufficiency, dyserythropoietic anemia, and calvarial hyperostosis
COX6B1	Cytochrome c oxidase subunit VIb polypeptide 1 (ubiquitous)	001863	124089	AR	Cytochrome c oxidase deficiency
CPT1A	Carnitine palmitoyltransferase 1, liver	001031847	600528	AR	Carnitine palmitoyltransferase IA deficiency
CPT2	Carnitine palmitoyltransferase 2	000098	600650	AR	Carnitine palmitoyltransferase II deficiency
CYCS	Cytochrome c, somatic	018947	123970	AD	Thrombocytopenia 4
DARS2	Aspartyl-tRNA synthetase 2, mitochondrial	018122	610956	AR	Leukoencephalopathy with brain stem and spinal cord involvement and lactate elevation
DBT	Dihydrolipoamide branched chain transacylase	001918	248610	AR	Maple syrup urine disease type 2

Table 3: Nuclear Genes Tested					
Gene Symbol	**Gene Description**	**NM #**	**OMIM #**	**Inh.**	**Commonly Associated Disorder(s)**
DGUOK	Deoxyguanosine kinase	080916	601465	AR	Mitochondrial DNA depletion syndrome
DLAT	Dihydrolipoamide S-acetyltransferase (E2 component of pyruvate dehydrogenase complex)	001931	608770	AR	Pyruvate dehydrogenase E2 deficiency
DLD	Dihydrolipoamide dehydrogenase (E3 component of pyruvate dehydrogenase complex, 2-oxo-glutarate complex, branched chain keto acid dehydrogenase complex)	000108	238331	AR	Dihydrolipoamide dehydrogenase deficiency
DNAJC19	DnaJ (Hsp40) homolog, subfamily C, member 19	145261	608977	AR	Dilated cardiomyopathy syndrome; 3-methylglutaconic aciduria type V
DNM1L	Dynamin 1-like	012062	603850	AR	Microcephaly, optic neuropathy and hypoplasia, lactic acidemia
ETFA	Electron-transferring-flavoprotein, alpha polypeptide	000126	608053	AR	Glutaric acidemia IIA
ETFB	Electron-transferring-flavoprotein, beta polypeptide	001985	130410	AR	Glutaric acidemia IIB
ETFDH	Electron-transferring-flavoprotein dehydrogenase	004453	231675	AR	Multiple acyl-CoA dehydrogenase deficiency (glutaric acidemia IIC)
ETHE1	Ethylmalonic encephalopathy 1	014297	608451	AR	Ethylmalonic encephalopathy
FASTKD2	FAST kinase domains 2	014929	612322	AR	Mitochondrial complex IV deficiency
FH	Fumarate hydratase	000143	136850	AR	Fumarate hydratase deficiency
				AD	Hereditary leiomyomatosis and renal cell cancer
FXN	Frataxin (FRDA)	001161706	606829	AR	Friedreich ataxia
GFER	Growth factor, augmenter of liver regeneration	005262	600924	AR	Progressive mitochondrial myopathy with congenital cataract, hearing loss, and developmental delay
GFM1	G elongation factor, mitochondrial 1	024996	606639	AR	Combined oxidative phosphorylation deficiency
HADH	Hydroxyacyl-Coenzyme A dehydrogenase (HADHSC)	005327	601609	AR	Hyperinsulinemic hypoglycemia
HADHA	Mitochondrial trifunctional protein, alpha subunit	000182	600890	AR	Mitochondrial trifunctional protein deficiency
HADHB	Mitochondrial trifunctional protein, beta subunit	000183	143450	AR	Mitochondrial trifunctional protein deficiency
HMGCL	3-hydroxyl-3-methylglutaryl coenzyme A lyase	000191	613898	AR	HMG-CoA lyase deficiency
HMGCS2	3-hydroxy-3-methylglutaryl-CoA synthase 2 (mitochondrial)	005518	600234	AR	HMG-CoA synthase deficiency
HSPD1	Heat shock 60kD protein 1 (chaperonin)	199440	118190	AD	Spastic paraplegia 13
				AR	Hypomyelinating leukodystrophy
ISCU	Iron-sulfur cluster scaffold homologue (E. coli)	014301	611911	AR	Hereditary myopathy with lactic acidosis
LARS2	Leucyl-tRNA synthetase 2, mitochondrial (KIAA0028)	015340	604544	AR	Perrault syndrome 4
LRPPRC	Leucine-rich PPR-motif containing	133259	607544	AR	Cytochrome c oxidase deficiency
MCCC2	Methylcrotonoyl-coenzyme A carboxylase 2 (beta)	022132	609014	AR	3-methylcrotonyl-CoA carboxylase deficiency
MFN2	Mitofusin 2	014874	608507	AD	Charcot-Marie-Tooth disease type 2A2
MPV17	Mpv17 transgene, murine homologue, glomerulosclerosis	002437	137960	AR	Mitochondrial DNA depletion syndrome 6 (hepatocerebral type)
MRPS16	Mitochondrial ribosomal protein S16	016065	609204	AR	Combined oxidative phosphorylation deficiency 2
MRPS22	Mitochondrial ribosomal protein S22	020191	605810	AR	Combined oxidative phosphorylation deficiency 5
NDUFA1	NADH dehydrogenase (ubiquinone) 1 alpha subcomplex, 1, 7.5kDa	004541	300078	XL	Mitochondrial complex I deficiency
NDUFA11	NADH dehydrogenase (ubiquinone) 1 alpha subcomplex, 11, 14.7kDa	001193375	612638	AR	Mitochondrial complex I deficiency

Table 3: Nuclear Genes Tested					
Gene Symbol	**Gene Description**	**NM #**	**OMIM #**	**Inh.**	**Commonly Associated Disorder(s)**
NDUFA2	NADH dehydrogenase (ubiquinone) 1 alpha subcomplex, 2, 8kDa	002488	602137	AR	Leigh syndrome due to mitochondrial complex I deficiency
NDUFAF1	NADH dehydrogenase (ubiquinone) 1 alpha subcomplex, assembly factor 1	016013	606934	AR	Mitochondrial complex I deficiency
NDUFAF2	NADH dehydrogenase (ubiquinone) 1 alpha subcomplex, assembly factor 2 (MMTN)	174889	609653	AR	Mitochondrial complex I deficiency
NDUFAF3	NADH dehydrogenase (ubiquinone) 1 alpha subcomplex, assembly factor 3	199073	612911	AR	Mitochondrial complex I deficiency
NDUFAF4	NADH dehydrogenase (ubiquinone) 1 alpha subcomplex, assembly factor 4	014165	611776	AR	Mitochondrial complex I deficiency
NDUFAF5	NADH dehydrogenase (ubiquinone) complex I, assembly factor 5	024120	612360	AR	Mitochondrial complex I deficiency
NDUFS1	NADH dehydrogenase (ubiquinone) Fe-S protein 1 (75kDa) (NADH-coenzyme Q reductase)	005006	157655	AR	Mitochondrial complex I deficiency
NDUFS2	NADH dehydrogenase (ubiquinone) Fe-S protein 2 (49kDa) (NADH-coenzyme Q reductase)	004550	602985	AR	Mitochondrial complex I deficiency
NDUFS3	NADH dehydrogenase (ubiquinone) Fe-S protein 3 (30kDa) (NADH-coenzyme Q reductase)	004551	603846	AR	Mitochondrial complex I deficiency
NDUFS4	NADH dehydrogenase (ubiquinone) Fe-S protein 4 (18kDa) (NADH-coenzyme Q reductase)	002495	602694	AR	Mitochondrial complex I deficiency
NDUFS6	NADH dehydrogenase (ubiquinone) Fe-S protein 6, 13kDa (NADH-coenzyme Q reductase)	004553	603848	AR	Mitochondrial complex I deficiency
NDUFS7	NADH dehydrogenase (ubiquinone) Fe-S protein 7 (20kDa) (NADH-coenzyme Q reductase)	024407	601825	AR	Mitochondrial complex I deficiency
NDUFS8	NADH dehydrogenase (ubiquinone) Fe-S protein 8 (23kDa) (NADH-coenzyme Q reductase)	002496	602141	AR	Mitochondrial complex I deficiency
NDUFV1	NADH dehydrogenase (ubiquinone) flavoprotein 1 (51kDa)	007103	161051	AR	Mitochondrial complex I deficiency
NDUFV2	NADH dehydrogenase (ubiquinone) flavoprotein 2 (24kDa)	021074	600532	AR	Mitochondrial complex I deficiency
OPA1	Optic atrophy 1 (autosomal dominant)	130837	605290	AD	Optic atrophy 1
OXCT1	3-oxoacid CoA transferase 1	000436	601424	AR	Succinyl CoA:3-oxoacid CoA transferase deficiency
PC	Pyruvate carboxylase	001040716	608786	AR	Pyruvate carboxylase deficiency
PCK2	Phosphoenolpyruvate carboxykinase 2 (mitochondrial)	004563	614095	Unknown	PEPCK deficiency, mitochondrial
PDHA1	Pyruvate dehydrogenase, E1 alpha polypeptide 1	000284	300502	XL	Pyruvate dehydrogenase E1-alpha deficiency
PDHB	Pyruvate dehydrogenase (lipoamide) beta	000925	179060	AR	Pyruvate dehydrogenase E1-beta deficiency
PDHX	Pyruvate dehydrogenase complex, component X (PDX1)	003477	608769	AR	Pyruvate dehydrogenase E3-binding protein deficiency
PDP1	Pyruvate dehydrogenase phosphatase catalytic subunit 1	018444	605993	AR	Pyruvate dehydrogenase phosphatase deficiency
PDSS1	Prenyl (decaprenyl) diphosphate synthase, subunit 1	014317	607429	AR	Coenzyme Q10 deficiency, primary, 2
PDSS2	Prenyl (decaprenyl) diphosphate synthase, subunit 2	020381	610564	AR	Coenzyme Q10 deficiency, primary, 3
PINK1	PTEN induced putative kinase 1	032409	608309	AR	Parkinson disease 6, early onset

Table 3: Nuclear Genes Tested					
Gene Symbol	**Gene Description**	**NM #**	**OMIM #**	**Inh.**	**Commonly Associated Disorder(s)**
POLG	Polymerase (DNA directed), gamma	002693	174763	AR/AD	Progressive external ophthalmoplegia (autosomal recessive or autosomal dominant), mitochondrial DNA depletion syndrome 4A (Alpers type) or 4B (MNGIE type)
POLG2	Polymerase (DNA directed), gamma 2, accessory subunit	007215	604983	AD	Progressive external ophthalmoplegia with mitochondrial DNA deletions, autosomal dominant, 4
PPM1B	Protein phosphatase, Mg2+/Mn2+ dependent, 1B	001033557	603770	Unknown	Mitochondrial disease
PREPL	Prolyl endopeptidase-like	001171603	609557	AR	PREPL deficiency
PUS1	Pseudouridylate synthase 1	025215	608109	AR	Mitochondrial myopathy and sideroblastic anemia 1
RARS2	Arginyl-tRNA synthetase 2, mitochondrial (putative)	020320	611524	AR	Pontocerebellar hypoplasia type 6
RRM2B	Ribonucleotide reductase M2 B (TP53 inducible)	015713	604712	AD/AR	Autosomal dominant progressive external ophthalmoplegia 5, mitochondrial DNA depletion syndrome 8A or 8B
SCO1	SCO (cytochrome oxidase deficient, yeast) homologue 1	004589	603644	AR	Mitochondrial complex IV deficiency
SCO2	SCO (cytochrome oxidase deficient, yeast) homologue 2	001169109	604272	AR	Fatal infantile cardioencephalomyopathy due to cytochrome c oxidase deficiency 1
SDHAF1	Succinate dehydrogenase complex assembly factor 1	001042631	612848	AR	Mitochondrial complex II deficiency
SDHB	Succinate dehydrogenase complex, subunit B, iron sulfur (Ip)	003000	185470	AR	Mitochondrial complex II deficiency
SDHC	Succinate dehydrogenase complex, subunit C, integral membrane protein, 15kDa	003001	602413	AR	Mitochondrial complex II deficiency
SDHD	Succinate dehydrogenase complex, subunit D, integral membrane protein	003002	602690	AR	Mitochondrial complex II deficiency
SLC22A5	Solute carrier family 22 (organic cation/carnitine transporter), member 5	003060	603377	AR	Systemic primary carnitine deficiency
SLC25A13	Solute carrier family 25, member 13 (citrin)	001160210	603859	AR	Adult-onset citrullinemia type II, neonatal- onset citrullinemia type II
SLC25A15	Solute carrier family 25 (mitochondrial carrier; ornithine transporter) member 15	014252	603861	AR	Hyperornithinemia-hyperammonemia- homocitrullinemia syndrome
SLC25A19	Solute carrier family 25 (mitochondrial thiamine pyrophosphate carrier), member 19	001126121	606521	AR	Amish type microcephaly, thiamine metabolism dysfunction syndrome 4
SLC25A20	Solute carrier family 25 (carnitine/acylcarnitine translocase), member 20	000387	613698	AR	Carnitine-acylcarnitine translocase deficiency
SLC25A22	Solute carrier family 25 (mitochondrial carrier: glutamate), member 22	024698	609302	AR	Early infantile epileptic encephalopathy 3
SLC25A3	Solute carrier family 25 (mitochondrial carrier; phosphate carrier), member 3	005888	600307	AR	Mitochondrial phosphate carrier deficiency
SLC25A4	Solute carrier family 25 (mitochondrial carrier; adenine nucleotide translocator), member 4	001151	103220	AD/AR	Autosomal dominant progressive external ophthalmoplegia with mitochondrial DNA deletions 2, mitochondrial DNA depletion syndrome 12
SLC3A1	Solute carrier family 3 (cystine, dibasic and neutral amino acid transporter), member 1	000341	104614	AR	Cystinuria
SPG7	Spastic paraplegia 7, paraplegin (pure and	003119	602783	AR	Autosomal recessive spastic paraplegia 7,

Table 3: Nuclear Genes Tested					
Gene Symbol	**Gene Description**	**NM #**	**OMIM #**	**Inh.**	**Commonly Associated Disorder(s)**
	complicated autosomal recessive)				chronic progressive external ophthalmoplegia
SUCLA2	Succinate-CoA ligase, ADP-forming, beta subunit	003850	603291	AR	Mitochondrial DNA depletion syndrome 5
SUCLG1	Succinate-CoA ligase, gdp-forming, alpha subunit	003849	611224	AR	Mitochondrial DNA depletion syndrome 9
SUOX	Sulphite oxidase	000456	606887	AR	Sulfite oxidase deficiency
SURF1	Surfeit 1	003172	185620	AR	Leigh syndrome due to mitochondrial complex IV deficiency
TAZ	Tafazzin (cardiomyopathy, dilated 3A [X-linked]; endocardial fibroelastosis 2; Barth syndrome)	000116	300394	XL	Barth syndrome
TIMM8A	Translocase of inner mitochondrial membrane 8 (yeast) homologue A (DFN1)	004085	300356	XL	Mohr-Tranebjaerg syndrome, Jensen syndrome, progressive XL deafness 1
TK2	Thymidine kinase 2, mitochondrial	004614	188250	AR	Mitochondrial DNA depletion syndrome 2
TMEM70	Transmembrane protein 70	017866	612418	AR	Mitochondrial complex V (ATP synthase) deficiency nuclear type 2
TRMU	trna 5-methylaminomethyl-2- thiouridylate methyltransferase	018006	610230	AR	Transient infantile liver failure, modifier of mitochondrial deafness
TSFM	Ts translation elongation factor, mitochondrial	001172697	604723	AR	Combined oxidative phosphorylation deficiency 3
TYMP	Thymidine phosphorylase (endothelial cell growth factor 1 (platelet-derived) ECGF1	001953	131222	AR	Mitochondrial DNA depletion syndrome 1 (MNGIE type)
UQCRB	Ubiquinol-cytochrome c reductase binding protein	006294	191330	AR	Mitochondrial complex III deficiency nuclear type 3
UQCRQ	Ubiquinol-cytochrome c reductase, complex III subunit VII, 9.5kDa	014402	612080	AR	Mitochondrial complex III deficiency nuclear type 4
WFS1	Wolfram syndrome 1 (wolframin)	006005	606201	AD/AR	Autosomal dominant deafness 6, Wolfram syndrome 1
AD, autosomal dominant; AR, autosomal recessive; Inh., inheritance; XL, X-linked					

Table 4: Risk for Inheriting Variants Causing Mitochondrial Disorders		
Variant Location	**Associated Inheritance Pattern**	**Risk to Family Members**

mtDNA	Maternal or sporadic	Single mtDNA deletions
		• Most often occur de novo
		• When transmitted, inherited from mother
		• No significant risk to parents/siblings
		mtDNA point variants or duplications
		• Typically inherited from the mother
		  ○ Mother may be clinically asymptomatic
		• Father of a proband is not at risk for carrying the variant
		• Females with heteroplasmy – variable amount of affected mitochondria passed to offspring
		  ○ Phenotypic variation within a family
		• Male and female offspring of females with variant at risk for inheriting the variant
		• Offspring of male variant carrier – not at risk for inheriting the variant

Nuclear DNA	Autosomal recessive	Offspring of carrier parents • 1 in 4 chance of being affected • 1 in 2 chance of being a carrier Offspring of affected individuals are all obligate carriers Unaffected sibling of an affected individual • 2 in 3 chance of being a carrier

Table 4: Risk for Inheriting Variants Causing Mitochondrial Disorders		
Variant Location	**Associated Inheritance Pattern**	**Risk to Family Members**
	Autosomal dominant	Offspring of affected individual • 1 in 2 chance of being affected Siblings of an affected individual • Risk depends on genetic status of the parents • If the proband inherited a variant from a parent, each sibling has a 1 in 2 chance of inheriting the variant
	X-linked recessive	Generally, males are affected and females are carriers • Asymptomatic mother of an affected male may have the same variant • De novo variants are possible If variant was maternally inherited • Male siblings have 1 in 2 chance of being affected • Female siblings have a 1 in 2 chance of being a carrier Offspring of males with variant • All females will be carriers • Males will not inherit the variant and will neither be carriers nor be affected