

Mitochondrial Disorders Panel (mtDNA Sequencing and Deletion/Duplication, 121 Nuclear Genes Sequencing, 119 Nuclear Genes 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

Test Description

- DNA enrichment of 121 targeted nuclear genes using capture DNA probes
- Mitochondrial genome (mtDNA) of 37 mtDNA genes is amplified by long-range polymerase chain reaction (LRPCR)
- Massively parallel sequencing
 - Reported variants are confirmed by Sanger sequencing
- Deletion/duplication analysis via custom comparative genomic hybridization (CGH) array of the mtDNA and 119 nuclear genes
 - Detects large deletions and duplications
 - Nuclear genes *LARS2* and *NDUFA2* are not included on the array
- Human genome build 19 (hg19) is used for data analysis

Tests to Consider

Primary test

[Mitochondrial Disorders Panel \(mtDNA by Sequencing and Deletion/Duplication, 121 Nuclear Genes by Sequencing, 119 Nuclear Genes by Deletion/Duplication\) 2006054](#)

- Preferred test for identifying deletions, duplications, and point variants in all 37 mitochondrial genes and in 121 nuclear genes known to cause mitochondrial disease

Related tests

[Mitochondrial Disorders \(mtDNA\) Sequencing 2006065](#)

- Assess for sequence variants in the 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 – individual's 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 (percentage of mutated vs. 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 copies of mtDNA are identical
 - Heteroplasmic
 - <99% of copies of mtDNA 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
 - 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*
- Not reported
 - Variants in the mitochondrial D-loop
 - Mosaic variants in nuclear genes

Table 1: Common Mitochondrial Syndromes

Disorder	Major Clinical Features	Inheritance	Commonly Associated Genes/Variants
Chronic progressive external ophthalmoplegia (CPEO)	<ul style="list-style-type: none"> • 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	<i>eg, C10orf2, OPA1, POLG, POLG2, RRM2, SLC25A4, SPG7, TYMP</i>
Kearns-Sayre syndrome (KSS)	<ul style="list-style-type: none"> • PEO onset <20 years of age • Pigmentary retinopathy • CSF protein >1g/L • Cerebellar ataxia • Heart block 	Sporadic (infrequently maternally transmitted)	mtDNA large deletions detected in ~90% of cases <ul style="list-style-type: none"> • m.8470_1344del4977 is most frequent
Leber hereditary optic neuropathy (LHON)	<ul style="list-style-type: none"> • 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 <ul style="list-style-type: none"> • <i>MT-ND4</i> m.11778G>A • <i>MT-ND6</i> m.14484T>C • <i>MT-ND1</i> m.3460G>A Variants in other mtDNA genes are rare causes of LHON
Leigh syndrome (LS)	<ul style="list-style-type: none"> • Progressive neurological disease with motor and intellectual developmental delay • Cerebellar and brain stem signs • Infantile onset 	Maternal	<ul style="list-style-type: none"> • mtDNA large deletions causative for <5% of LS • <i>MT-ATP6</i> (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)
Mitochondrial encephalomyopathy with lactic acidosis and stroke-like episodes (MELAS)	<ul style="list-style-type: none"> • 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	<i>MT-TL1</i> (accounts for majority of cases) <ul style="list-style-type: none"> • m.3243A>G • m.3271T>C • m.3252A>G <i>MT-ND5</i> <ul style="list-style-type: none"> • m.13513G>A Variants in other mtDNA genes are rare

Disorder	Major Clinical Features	Inheritance	Commonly Associated Genes/Variants
Myoclonic epilepsy with ragged-red fibers (MERRF)	<ul style="list-style-type: none"> • Myoclonus • Seizures • Cerebellar ataxia • Myopathy 	Maternal	<i>MT-TK</i> (accounts for ~90% of cases) <ul style="list-style-type: none"> • m.8344A>G • m.8356T>C • m.8363G>A • m.8361G>A Causative variants in other mtDNA genes, including <i>MT-TP</i> and <i>MT-TF</i> , account for <5% of cases
Neurogenic weakness with ataxia and retinitis pigmentosa (NARP)	<ul style="list-style-type: none"> • Late-childhood or adult-onset peripheral neuropathy • Ataxia • Pigmentary retinopathy 	Maternal	<i>MT-ATP6</i> (estimated to account for >50% of cases) <ul style="list-style-type: none"> • m.8993T>G • m.8993T>C
Pearson syndrome	<ul style="list-style-type: none"> • Sideroblastic anemia of childhood • Pancytopenia • Exocrine pancreatic failure 	Sporadic (infrequently maternally transmitted)	mtDNA large deletions

Table 2: Mitochondrial DNA (mtDNA) Genes¹ Tested

Gene Symbol	Gene Description	OMIM #	Inheritance
<i>MT-ATP6</i>	Mitochondrially encoded ATP synthase 6 (overlaps <i>MT-ATP8</i> gene)	516060	Maternal
<i>MT-ATP8</i>	Mitochondrially encoded ATP synthase 8 (overlaps <i>MT-ATP6</i> gene)	516070	Maternal
<i>MT-CO1</i>	Mitochondrially encoded cytochrome c oxidase I	516030	Maternal
<i>MT-CO2</i>	Mitochondrially encoded cytochrome c oxidase II	516040	Maternal
<i>MT-CO3</i>	Mitochondrially encoded cytochrome c oxidase III	516050	Maternal
<i>MT-CYB</i>	Mitochondrially encoded cytochrome b	516020	Maternal
<i>MT-ND1</i>	Mitochondrially encoded NADH dehydrogenase 1	516000	Maternal
<i>MT-ND2</i>	Mitochondrially encoded NADH dehydrogenase 2	516001	Maternal
<i>MT-ND3</i>	Mitochondrially encoded NADH dehydrogenase 3	516002	Maternal
<i>MT-ND4</i>	Mitochondrially encoded NADH dehydrogenase 4	516003	Maternal
<i>MT-ND4L</i>	Mitochondrially encoded NADH dehydrogenase 4L	516004	Maternal
<i>MT-ND5</i>	Mitochondrially encoded NADH dehydrogenase 5	516005	Maternal
<i>MT-ND6</i>	Mitochondrially encoded NADH dehydrogenase 6	516006	Maternal
<i>MT-RNR1</i>	Mitochondrially encoded 12S RNA	561000	Maternal
<i>MT-RNR2</i>	Mitochondrially encoded 16S RNA	561010	Maternal
<i>MT-TA</i>	Mitochondrially encoded tRNA alanine	590000	Maternal
<i>MT-TC</i>	Mitochondrially encoded tRNA cysteine	590020	Maternal
<i>MT-TD</i>	Mitochondrially encoded tRNA aspartic acid	590015	Maternal
<i>MT-TE</i>	Mitochondrially encoded tRNA glutamic acid	590025	Maternal
<i>MT-TF</i>	Mitochondrially encoded tRNA phenylalanine	590070	Maternal
<i>MT-TG</i>	Mitochondrially encoded tRNA glycine	590035	Maternal
<i>MT-TH</i>	Mitochondrially encoded tRNA histidine	590040	Maternal
<i>MT-TI</i>	Mitochondrially encoded tRNA isoleucine	590045	Maternal
<i>MT-TK</i>	Mitochondrially encoded tRNA lysine	590060	Maternal
<i>MT-TL1</i>	Mitochondrially encoded tRNA leucine 1 (UUA/G)	590050	Maternal
<i>MT-TL2</i>	Mitochondrially encoded tRNA leucine 2 (CUN)	590055	Maternal
<i>MT-TM</i>	Mitochondrially encoded tRNA methionine	590065	Maternal
<i>MT-TN</i>	Mitochondrially encoded tRNA asparagine	590010	Maternal
<i>MT-TP</i>	Mitochondrially encoded tRNA proline	590075	Maternal
<i>MT-TQ</i>	Mitochondrially encoded tRNA glutamine	590030	Maternal
<i>MT-TR</i>	Mitochondrially encoded tRNA arginine	590005	Maternal
<i>MT-TS1</i>	Mitochondrially encoded tRNA serine 1 (UCN)	590080	Maternal
<i>MT-TS2</i>	Mitochondrially encoded tRNA serine 2 (AGU/C)	590085	Maternal
<i>MT-TT</i>	Mitochondrially encoded tRNA threonine	590090	Maternal
<i>MT-TV</i>	Mitochondrially encoded tRNA valine	590105	Maternal
<i>MT-TW</i>	Mitochondrially encoded tRNA tryptophan	590095	Maternal
<i>MT-TY</i>	Mitochondrially encoded tRNA tyrosine	590100	Maternal

¹All mitochondrial genes are reference sequence NC_012920

Table 3: Nuclear Genes Tested

Gene Symbol	Gene Description	NM #	OMIM #	Inh.	Commonly Associated Disorder(s)
<i>ABCB7</i>	ATP-binding cassette, sub-family B (MDR/TAP), member 7	004299	300135	XL	Sideroblastic anemia and ataxia
<i>ACAD9</i>	acyl-Coenzyme A dehydrogenase family, member 9	014049	611103	AR	Complex 1 deficiency, ACAD9 deficiency
<i>ACADL</i>	acyl-CoA dehydrogenase, long chain	001608	609576	Unknown	LCAD deficiency
<i>ACADM</i>	acyl-CoA dehydrogenase, medium chain	000016	607008	AR	MCAD deficiency
<i>ACADS</i>	acyl-CoA dehydrogenase, short chain	000017	606885	AR	SCAD deficiency
<i>ACADVL</i>	Very long chain acyl-CoA dehydrogenase	000018	609575	AR	VLCAD deficiency
<i>ACAT1</i>	Acetoacetyl 1-CoA thiolase	000019	607809	AR	Acetoacetyl-CoA-thiolase deficiency
<i>ADCK3</i>	aarF domain containing kinase 3	020247	606980	AR	Ubiquinone deficiency with cerebellar ataxia
<i>APTX</i>	Aprataxin	175073	606350	AR	Ataxia-ocular apraxia 1
<i>ASS1</i>	Argininosuccinate synthetase	000050	603470	AR	Citrullinemia type I
<i>ATPAF2</i>	ATP synthase mitochondrial F1 complex assembly factor 2	145691	608918	AR	Complex V deficiency
<i>BCKDHA</i>	Branched chain keto acid dehydrogenase E1, alpha polypeptide	000709	608348	AR	Maple syrup urine disease type 1A
<i>BCKDHB</i>	Branched chain keto acid dehydrogenase E1, beta polypeptide	183050	248611	AR	Maple syrup urine disease type 1B
<i>BCS1L</i>	BCS1 (yeast homologue)-like	004328	603647	AR	Complex 3 deficiency
<i>C10orf2</i>	Chromosome 10 open reading frame 2	021830	606075	AD/AR	Infantile-onset spinocerebellar ataxia, progressive external ophthalmoplegia
<i>COQ2</i>	Coenzyme Q2 homologue, prenyltransferase (yeast)	015697	609825	AR	Primary coenzyme Q10 deficiency 1
<i>COQ9</i>	Coenzyme Q9 homolog (<i>S. cerevisiae</i>)	020312	612837	AR	Primary coenzyme Q10 deficiency
<i>COX10</i>	COX10 (yeast) homologue, cytochrome C oxidase assembly protein (haem A: farnesyltransferase)	001303	602125	AR	Cytochrome c oxidase deficiency
<i>COX15</i>	COX15 homologue, cytochrome c oxidase assembly protein (yeast)	078470	603646	AR	Cytochrome c oxidase deficiency 2, Leigh syndrome
<i>COX4I2</i>	Cytochrome c oxidase subunit IV isoform 2 (lung)	032609	607976	AR	Exocrine pancreatic insufficiency, dyserythropoietic anemia, and calvarial hyperostosis
<i>COX6B1</i>	Cytochrome c oxidase subunit VIb polypeptide 1 (ubiquitous)	001863	124089	AR	Cytochrome c oxidase deficiency
<i>CPT1A</i>	Carnitine palmitoyltransferase 1, liver	001876	600528	AR	Carnitine palmitoyltransferase IA deficiency
<i>CPT2</i>	Carnitine palmitoyltransferase 2	000098	600650	AR	Carnitine palmitoyltransferase II deficiency
<i>CYCS</i>	Cytochrome c, somatic	018947	123970	AD	Thrombocytopenia 4
<i>DARS2</i>	Aspartyl-tRNA synthetase 2, mitochondrial	018122	610956	AR	Leukoencephalopathy with brain stem and spinal cord involvement and lactate elevation
<i>DBT</i>	Dihydrolipoamide branched chain transacylase	001918	248610	AR	Maple syrup urine disease type 2
<i>DGUOK</i>	Deoxyguanosine kinase	080916	601465	AR	Mitochondrial DNA depletion syndrome
<i>DLAT</i>	Dihydrolipoamide S-acetyltransferase (E2 component of pyruvate dehydrogenase complex)	001931	608770	AR	Pyruvate dehydrogenase E2 deficiency
<i>DLD</i>	Dihydrolipoamide dehydrogenase (E3 component of pyruvate dehydrogenase complex, 2-oxo-glutarate complex, branched chain keto acid dehydrogenase complex)	000108	238331	AR	Dihydrolipoamide dehydrogenase deficiency
<i>DNAJC19</i>	Dnaj (Hsp40) homolog, subfamily C, member 19	145261	608977	AR	Dilated cardiomyopathy syndrome; 3-methylglutaconic aciduria type V
<i>DNM1L</i>	Dynamamin 1-like	012062	603850	AR	Microcephaly, optic neuropathy and hypoplasia, lactic acidemia

Gene Symbol	Gene Description	NM #	OMIM #	Inh.	Commonly Associated Disorder(s)
<i>ETFA</i>	Electron-transferring-flavoprotein, alpha polypeptide	000126	608053	AR	Glutaric acidemia IIA
<i>ETFB</i>	Electron-transferring-flavoprotein, beta polypeptide	001014763	130410	AR	Glutaric acidemia IIB
<i>ETFDH</i>	Electron-transferring-flavoprotein dehydrogenase	004453	231675	AR	Multiple acyl-CoA dehydrogenase deficiency (glutaric acidemia IIC)
<i>ETHE1</i>	Ethylmalonic encephalopathy 1	014297	608451	AR	Ethylmalonic encephalopathy
<i>FASTKD2</i>	FAST kinase domains 2	001136194	612322	AR	Mitochondrial complex IV deficiency
<i>FH</i>	Fumarate hydratase	000143	136850	AR	Fumarate hydratase deficiency
				AD	Hereditary leiomyomatosis and renal cell cancer
<i>FXN</i>	Frataxin (FRDA)	000144	606829	AR	Friedreich ataxia
<i>GFER</i>	Growth factor, augments of liver regeneration	005262	600924	AR	Progressive mitochondrial myopathy with congenital cataract, hearing loss, and developmental delay
<i>GFM1</i>	G elongation factor, mitochondrial 1	024996	606639	AR	Combined oxidative phosphorylation deficiency
<i>HADH</i>	Hydroxyacyl-Coenzyme A dehydrogenase (HADHSC)	001184705	601609	AR	Hyperinsulinemic hypoglycemia
<i>HADHA</i>	Mitochondrial trifunctional protein, alpha subunit	000182	600890	AR	Mitochondrial trifunctional protein deficiency
<i>HADHB</i>	Mitochondrial trifunctional protein, beta subunit	000183	143450	AR	Mitochondrial trifunctional protein deficiency
<i>HMGCL</i>	3-hydroxy-3-methylglutaryl coenzyme A lyase	000191	613898	AR	HMG-CoA lyase deficiency
<i>HMGCS2</i>	3-hydroxy-3-methylglutaryl-CoA synthase 2 (mitochondrial)	005518	600234	AR	HMG-CoA synthase deficiency
<i>HSPD1</i>	Heat shock 60kD protein 1 (chaperonin)	002156	118190	AD	Spastic paraplegia 13
				AR	Hypomyelinating leukodystrophy
<i>ISCU</i>	Iron-sulfur cluster scaffold homologue (E. coli)	014301	611911	AR	Hereditary myopathy with lactic acidosis
<i>LARS2</i>	Leucyl-tRNA synthetase 2, mitochondrial (KIAA0028)	015340	604544	AR	Perrault syndrome 4
<i>LRPPRC</i>	Leucine-rich PPR-motif containing	133259	607544	AR	Cytochrome c oxidase deficiency
<i>MCCC2</i>	Methylcrotonoyl-coenzyme A carboxylase 2 (beta)	022132	609014	AR	3-methylcrotonyl-CoA carboxylase deficiency
<i>MFN2</i>	Mitofusin 2	014874	608507	AD	Charcot-Marie-Tooth disease type 2A2
<i>MPV17</i>	Mpv17 transgene, murine homologue, glomerulosclerosis	002437	137960	AR	Mitochondrial DNA depletion syndrome 6 (hepatocerebral type)
<i>MRPS16</i>	Mitochondrial ribosomal protein S16	016065	609204	AR	Combined oxidative phosphorylation deficiency 2
<i>MRPS22</i>	Mitochondrial ribosomal protein S22	020191	605810	AR	Combined oxidative phosphorylation deficiency 5
<i>NDUFA1</i>	NADH dehydrogenase (ubiquinone) 1 alpha subcomplex, 1, 7.5kDa	004541	300078	XL	Mitochondrial complex I deficiency
<i>NDUFA11</i>	NADH dehydrogenase (ubiquinone) 1 alpha subcomplex, 11, 14.7kDa	175614	612638	AR	Mitochondrial complex I deficiency
<i>NDUFA2</i>	NADH dehydrogenase (ubiquinone) 1 alpha subcomplex, 2, 8kDa	002488	602137	AR	Leigh syndrome due to mitochondrial complex I deficiency
<i>NDUFAF1</i>	NADH dehydrogenase (ubiquinone) 1 alpha subcomplex, assembly factor 1	016013	606934	AR	Mitochondrial complex I deficiency
<i>NDUFAF2</i>	NADH dehydrogenase (ubiquinone) 1 alpha subcomplex, assembly factor 2 (MMTN)	174889	609653	AR	Mitochondrial complex I deficiency
<i>NDUFAF3</i>	NADH dehydrogenase (ubiquinone) 1 alpha subcomplex, assembly factor 3	199069	612911	AR	Mitochondrial complex I deficiency
<i>NDUFAF4</i>	NADH dehydrogenase (ubiquinone) 1 alpha subcomplex, assembly factor 4	014165	611776	AR	Mitochondrial complex I deficiency
<i>NDUFAF5</i>	NADH dehydrogenase (ubiquinone) complex I, assembly factor 5	024120	612360	AR	Mitochondrial complex I deficiency

Gene Symbol	Gene Description	NM #	OMIM	Inh.	Commonly Associated Disorder(s)
<i>NDUFS1</i>	NADH dehydrogenase (ubiquinone) Fe-S protein 1 (75kDa) (NADH-coenzyme Q reductase)	005006	157655	AR	Mitochondrial complex I deficiency
<i>NDUFS2</i>	NADH dehydrogenase (ubiquinone) Fe-S protein 2 (49kDa) (NADH-coenzyme Q reductase)	004550	602985	AR	Mitochondrial complex I deficiency
<i>NDUFS3</i>	NADH dehydrogenase (ubiquinone) Fe-S protein 3 (30kDa) (NADH-coenzyme Q reductase)	004551	603846	AR	Mitochondrial complex I deficiency
<i>NDUFS4</i>	NADH dehydrogenase (ubiquinone) Fe-S protein 4 (18kDa) (NADH-coenzyme Q reductase)	002495	602694	AR	Mitochondrial complex I deficiency
<i>NDUFS6</i>	NADH dehydrogenase (ubiquinone) Fe-S protein 6, 13kDa (NADH-coenzyme Q reductase)	004553	603848	AR	Mitochondrial complex I deficiency
<i>NDUFS7</i>	NADH dehydrogenase (ubiquinone) Fe-S protein 7 (20kDa) (NADH-coenzyme Q reductase)	024407	601825	AR	Mitochondrial complex I deficiency
<i>NDUFS8</i>	NADH dehydrogenase (ubiquinone) Fe-S protein 8 (23kDa) (NADH-coenzyme Q reductase)	002496	602141	AR	Mitochondrial complex I deficiency
<i>NDUFV1</i>	NADH dehydrogenase (ubiquinone) flavoprotein 1 (51kDa)	007103	161051	AR	Mitochondrial complex I deficiency
<i>NDUFV2</i>	NADH dehydrogenase (ubiquinone) flavoprotein 2 (24kDa)	021074	600532	AR	Mitochondrial complex I deficiency
<i>OPA1</i>	Optic atrophy 1 (autosomal dominant)	130837	605290	AD	Optic atrophy 1
<i>OXCT1</i>	3-oxoacid CoA transferase 1	000436	601424	AR	Succinyl CoA:3-oxoacid CoA transferase deficiency
<i>PC</i>	Pyruvate carboxylase	000920	608786	AR	Pyruvate carboxylase deficiency
<i>PCK2</i>	Phosphoenolpyruvate carboxykinase 2 (mitochondrial)	004563	614095	Unknown	PEPCK deficiency, mitochondrial
<i>PDHA1</i>	Pyruvate dehydrogenase, E1 alpha polypeptide 1	001173454	300502	XL	Pyruvate dehydrogenase E1-alpha deficiency
<i>PDHB</i>	Pyruvate dehydrogenase (lipoamide) beta	000925	179060	AR	Pyruvate dehydrogenase E1-beta deficiency
<i>PDHX</i>	Pyruvate dehydrogenase complex, component X (PDX1)	003477	608769	AR	Pyruvate dehydrogenase E3-binding protein deficiency
<i>PDP1</i>	Pyruvate dehydrogenase phosphatase catalytic subunit 1	018444	605993	AR	Pyruvate dehydrogenase phosphatase deficiency
<i>PDSS1</i>	Prenyl (decaprenyl) diphosphate synthase, subunit 1	014317	607429	AR	Coenzyme Q10 deficiency, primary, 2
<i>PDSS2</i>	Prenyl (decaprenyl) diphosphate synthase, subunit 2	020381	610564	AR	Coenzyme Q10 deficiency, primary, 3
<i>PINK1</i>	PTEN induced putative kinase 1	032409	608309	AR	Parkinson disease 6, early onset
<i>POLG</i>	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)
<i>POLG2</i>	Polymerase (DNA directed), gamma 2, accessory subunit	007215	604983	AD	Progressive external ophthalmoplegia with mitochondrial DNA deletions, autosomal dominant, 4
<i>PPM1B</i>	Protein phosphatase, Mg ²⁺ /Mn ²⁺ dependent, 1B	002706	603770	Unknown	Mitochondrial disease
<i>PREPL</i>	Prolyl endopeptidase-like	006036	609557	AR	PREPL deficiency
<i>PUS1</i>	Pseudouridylate synthase 1	025215	608109	AR	Mitochondrial myopathy and sideroblastic anemia 1
<i>RARS2</i>	Arginyl-tRNA synthetase 2, mitochondrial (putative)	020320	611524	AR	Pontocerebellar hypoplasia type 6

Gene Symbol	Gene Description	NM #	OMIM	Inh.	Commonly Associated Disorder(s)
<i>RRM2B</i>	Ribonucleotide reductase M2 B (TP53 inducible)	015713	604712	AD/AR	Autosomal dominant progressive external ophthalmoplegia 5, mitochondrial DNA depletion syndrome 8A or 8B
<i>SCO1</i>	SCO (cytochrome oxidase deficient, yeast) homologue 1	004589	603644	AR	Mitochondrial complex IV deficiency
<i>SCO2</i>	SCO (cytochrome oxidase deficient, yeast) homologue 2	005138	604272	AR	Fatal infantile cardioencephalomyopathy due to cytochrome c oxidase deficiency 1
<i>SDHAF1</i>	Succinate dehydrogenase complex assembly factor 1	001042631	612848	AR	Mitochondrial complex II deficiency
<i>SDHB</i>	Succinate dehydrogenase complex, subunit B, iron sulfur (Ip)	003000	185470	AR	Mitochondrial complex II deficiency
<i>SDHC</i>	Succinate dehydrogenase complex, subunit C, integral membrane protein, 15kDa	003001	602413	AR	Mitochondrial complex II deficiency
<i>SDHD</i>	Succinate dehydrogenase complex, subunit D, integral membrane protein	003002	602690	AR	Mitochondrial complex II deficiency
<i>SLC22A5</i>	Solute carrier family 22 (organic cation/carnitine transporter), member 5	003060	603377	AR	Systemic primary carnitine deficiency
<i>SLC25A13</i>	Solute carrier family 25, member 13 (citrin)	001160210	603859	AR	Adult-onset citrullinemia type II, neonatal-onset citrullinemia type II
<i>SLC25A15</i>	Solute carrier family 25 (mitochondrial carrier; ornithine transporter) member 15	014252	603861	AR	Hyperornithinemia-hyperammonemia-homocitrullinemia syndrome
<i>SLC25A19</i>	Solute carrier family 25 (mitochondrial thiamine pyrophosphate carrier), member 19	001126121	606521	AR	Amish type microcephaly, thiamine metabolism dysfunction syndrome 4
<i>SLC25A20</i>	Solute carrier family 25 (carnitine/acylcarnitine translocase), member 20	000387	613698	AR	Carnitine-acylcarnitine translocase deficiency
<i>SLC25A22</i>	Solute carrier family 25 (mitochondrial carrier: glutamate), member 22	024698	609302	AR	Early infantile epileptic encephalopathy 3
<i>SLC25A3</i>	Solute carrier family 25 (mitochondrial carrier; phosphate carrier), member 3	002635	600307	AR	Mitochondrial phosphate carrier deficiency
<i>SLC25A4</i>	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
<i>SLC3A1</i>	Solute carrier family 3 (cystine, dibasic and neutral amino acid transporter), member 1	000341	104614	AR	Cystinuria
<i>SPG7</i>	Spastic paraplegia 7, paraplegin (pure and complicated autosomal recessive)	003119	602783	AR	Autosomal recessive spastic paraplegia 7, chronic progressive external ophthalmoplegia
<i>SUCLA2</i>	Succinate-CoA ligase, ADP-forming, beta subunit	003850	603291	AR	Mitochondrial DNA depletion syndrome 5
<i>SUCLG1</i>	Succinate-CoA ligase, gdp-forming, alpha subunit	003849	611224	AR	Mitochondrial DNA depletion syndrome 9
<i>SUOX</i>	Sulphite oxidase	000456	606887	AR	Sulfite oxidase deficiency
<i>SURF1</i>	Surfeit 1	003172	185620	AR	Leigh syndrome due to mitochondrial complex IV deficiency
<i>TAZ</i>	Tafazzin (cardiomyopathy, dilated 3A (X-linked); endocardial fibroelastosis 2; Barth syndrome)	000116	300394	XL	Barth syndrome
<i>TIMM8A</i>	Translocase of inner mitochondrial membrane 8 (yeast) homologue A (DFN1)	004085	300356	XL	Mohr-Tranebjaerg syndrome, Jensen syndrome, progressive XL deafness 1
<i>TK2</i>	Thymidine kinase 2, mitochondrial	004614	188250	AR	Mitochondrial DNA depletion syndrome 2
<i>TMEM70</i>	Transmembrane protein 70	017866	612418	AR	Mitochondrial complex V (ATP synthase) deficiency nuclear type 2
<i>TMPO</i>	Thymopoietin	001032283	188380	AD	Dilated cardiomyopathy 1T
<i>TRMU</i>	trna 5-methylaminomethyl-2-thiouridylate methyltransferase	018006	610230	AR	Transient infantile liver failure, modifier of mitochondrial deafness

Gene Symbol	Gene Description	NM #	OMIM #	Inh.	Commonly Associated Disorder(s)
<i>TSFM</i>	Ts translation elongation factor, mitochondrial	001172696	604723	AR	Combined oxidative phosphorylation deficiency 3
<i>TUFM</i>	Tu translation elongation factor, mitochondrial	003321	602389	AR	Combined oxidative phosphorylation deficiency 4
<i>TYMP</i>	Thymidine phosphorylase (endothelial cell growth factor 1 (platelet-derived) ECGF1	001113755	131222	AR	Mitochondrial DNA depletion syndrome 1 (MNGIE type)
<i>UQCRB</i>	Ubiquinol-cytochrome c reductase binding protein	006294	191330	AR	Mitochondrial complex III deficiency nuclear type 3
<i>UQCRCQ</i>	Ubiquinol-cytochrome c reductase, complex III subunit VII, 9.5kDa	014402	612080	AR	Mitochondrial complex III deficiency nuclear type 4
<i>WFS1</i>	Wolfram syndrome 1 (wolframin)	006005	606201	AD/AR	Autosomal dominant deafness 6, Wolfram syndrome 1

Inh. = inheritance; AD = autosomal dominant; AR = autosomal recessive; 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	<p>Single mtDNA deletions</p> <ul style="list-style-type: none"> • Most often occur de novo • When transmitted, inherited from mother • No significant risk to parents/siblings <p>mtDNA point variants or duplications</p> <ul style="list-style-type: none"> • Typically inherited from the mother <ul style="list-style-type: none"> ◦ 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 <ul style="list-style-type: none"> ◦ 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	<p>Offspring of carrier parents</p> <ul style="list-style-type: none"> • 1 in 4 chance of being affected • 1 in 2 chance of being a carrier • Offspring of affected individuals • All are obligate carriers <p>Unaffected sibling of an affected individual</p> <ul style="list-style-type: none"> • 2 in 3 chance of being a carrier
	Autosomal dominant	<p>Offspring of affected individual</p> <ul style="list-style-type: none"> • 1 in 2 chance of being affected <p>Siblings of an affected individual</p> <ul style="list-style-type: none"> • 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	<p>Generally, males are affected and females are carriers</p> <ul style="list-style-type: none"> • Asymptomatic mother of an affected male may have the same variant • De novo variants are possible <p>If variant was maternally inherited</p> <ul style="list-style-type: none"> • Male siblings have 1 in 2 chance of being affected • Female siblings have a 1 in 2 chance of being a carrier <p>Offspring of males with variant</p> <ul style="list-style-type: none"> • All females will be carriers • Males will not inherit the variant and will neither be carriers nor be affected