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Mitochondrial Disorders Panel

Mitochondrial disorders originate from variants in nuclear DNA or mitochondrial DNA (mtDNA) and result in a spectrum of pathological conditions. Some disorders affect single organs (eg, eye, ear), while others affect multiple systems.

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 and 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).

See Common Mitochondrial Syndromes table below.

Inheritance

Variable, dependent on the gene(s) involved

- 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 DESCRIPTION

See Genes Tested tables for mtDNA and nuclear genes included in the panel.

Clinical Sensitivity

Variable, dependent on phenotype/condition

TESTS TO CONSIDER

Mitochondrial Disorders Panel (mtDNA Sequencing, Nuclear Genes Sequencing, and Deletion/Duplication) (Temporary Referral as of 01/08/2019) 2006054
Method: Massively Parallel Sequencing/Exonic Oligonucleotide-Based CGH Microarray

Indications for testing:

- Preferred test to confirm a suspected diagnosis of a mitochondrial disorder caused by a mitochondrial genome (mtDNA) sequence variant or variant(s) in related nuclear genes in individuals with:
  - Complex neurological features or a single neurological symptom and other system involvement
  - Progressive multisystem disorder of unknown etiology

Mitochondrial Disorders (mtDNA) Sequencing (Temporary Referral as of 01/08/2019) 2006065
Method: Massively Parallel Sequencing

Indications for testing:

- Assess for sequence variants in the mitochondrial genome (mtDNA) causing mitochondrial disorders, especially for individuals with clinical symptoms characteristic of a specific disorder, such as:
  - Leber hereditary optic neuropathy (LHON)
  - Mitochondrial encephalomyopathy with lactic acidosis and stroke-like episodes (MELAS)
  - Myoclonic epilepsy with ragged-red fibers (MERRF)
  - Neurogenic weakness with ataxia and retinitis pigmentosa (NARP)

Limitations

- A negative result does not exclude a mitochondrial disorder.
- Diagnostic errors can occur due to rare sequence variations.
- Interpretation of this test result may be impacted if this individual has had an allogeneic stem cell transplantation.
- The following will not be evaluated:
  - Variants outside the coding regions and intron-exon boundaries of the targeted genes
  - Regulatory region variants and deep intronic variants
  - Breakpoints of large deletions/duplications
  - Deletion/duplication analysis of the mitochondrial genome
  - Deletions/duplications in *FBXL4, FOXRED1, LARS2, NDUFA2, NDUFAF2, NUBPL, OPA3, TAZ*
  - Variants in the mitochondrial genome D-loop and mosaic variants in nuclear genes
  - Noncoding transcripts
  - The following exons are not sequenced due to technical limitations of the assay:
    - *COX10* (NM_001303) 6
    - *HSPD1* (NM_002156) 12
    - *PDSS1* (NM_014317) 2
    - *SDHC* (NM_001035511) 5
    - *SDHD* (NM_001276506) 4
- The following may not be detected:
  - Deletions/duplications/insertions of any size by massively parallel sequencing
  - Deletions/duplications less than 1kb in the targeted nuclear genes by array
  - Some variants due to technical limitations in the presence of pseudogenes, repetitive, or homologous regions
  - Low-level somatic variants
  - Variants in the mitochondrial genome present at less than 10 percent heteroplasmy
    - Homoplasmy is defined as greater than or equal to 99 percent of mitochondrial genome sequences identical and heteroplasmy as less than 99 percent of sequences identical
    - The percentage of heteroplasmy will not be reported
  - Single exon deletions/duplications in the following exons:

Gene	Exon(s)
ACAD9	(NM_014049) 10
ACADM	(NM_000016) 1, 12
ACADM	(NM_001286042) 1
ACADS	(NM_000017) 1, 9
ACADVL	(NM_000018) 1, 2, 17
APTX	(NM_175073) 9
ASS1	(NM_000050) 9, 15
COQ8A	(NM_020247) 5, 10
COQ9	(NM_020312) 1, 9
COX10	(NM_001303) 6
COX15	(NM_001320974) 9
DNAJC19	(NM_145261) 1
ETFA	(NM_000126) 1
ETFB	(NM_001985) 3
ETFDH	(NM_004453) 13

Familial Mutation, Targeted Sequencing 2001961
Method: Polymerase Chain Reaction/Sequencing

Indication for testing:

- Recommended test if there is a known familial sequence variant previously identified in a family member.
- A copy of the family member's test result documenting the familial variant is required.

The above tests do not assess for large deletions in the mitochondrial genome; thus, **ARE NOT RECOMMENDED** for the following indications:

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

Gene	Exon(s)
ETHE1	(NM_001320868) 2
ETHE1	(NM_014297) 1, 2
FH	(NM_000143) 1
GFM1	(NM_001308164) 6
HADH	(NM_001331027) 1
HMGCL	(NM_000191) 1, 6
LRPPRC	(NM_133259) 1
MCCC2	(NM_022132) 1
MRPS16	(NM_016065) 1
NDUFAF3	(NM_199069) 1
NDUFAF5	(NM_024120) 4
NDUFS7	(NM_024407) 4, 6, 7
NDUFS8	(NM_002496) 5
NDUFV1	(NM_001166102) 1
NDUFV1	(NM_007103) 1, 10
PCK2	(NM_004563) 1
PDHA1	(NM_000284) 1, 9
PDHA1	(NM_001173454) 2
PDHB	(NM_000925) 2
PDSS1	(NM_014317) 1, 2
PUS1	(NM_025215) 1
RARS2	(NM_020320) 4, 19
SDHD	(NM_001276506) 4
SLC25A13	(NM_014251) 1
SLC25A22	(NM_024698) 5
SPG7	(NM_003119) 1, 3
SUCLA2	(NM_003850) 6, 11
SURF1	(NM_003172) 1, 2
TK2	(NM_001271934) 3
TK2	(NM_004614) 1
TRMU	(NM_018006) 1
TSFM	(NM_001172696) 5
TUFM	(NM_003321) 1
TYMP	(NM_001953) 2, 8, 9, 10

Analytical Sensitivity

For nuclear genes by massively parallel sequencing:

Variant Class	Analytical Sensitivity (PPA Estimate[a] (%)	Analytical Sensitivity (PPA) 95% Credibility Region[a] (%)
SNVs	99.2	96.9-99.4

Variant Class	Analytical Sensitivity (PPA Estimate[a] (%)	Analytical Sensitivity (PPA) 95% Credibility Region[a] (%)
Deletions 1-10 bp	93.8	84.3-98.2
Deletions 11-44 bp	100	87.8-100
Insertions 1-10 bp	94.8	86.8-98.5
Insertions 11-23 bp	100	62.1-100

[a]Genes included on this test are a subset of a larger methods-based validation from which the PPA values are derived.

bp, base pairs; PPA, positive percent agreement; SNVs, single nucleotide variants

Common Mitochondrial Disorders

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, *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 cause ~10% 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)
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

Disorder	Major Clinical Features	Inheritance	Commonly Associated Genes/Variants
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-TF*, *MT-TL1, MT-TI,* and *MT-TP* 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

Genes Tested

Mitochondrial DNA (mtDNA) Genes	
Gene Symbol	**MIM #**
MT-ATP6	516060
MT-ATP8	516070
MT-CO1	516030
MT-CO2	516040
MT-CO3	516050
MT-CYB	516020
MT-ND1	516000
MT-ND2	516001
MT-ND3	516002
MT-ND4	516003
MT-ND4L	516004
MT-ND5	516005
MT-ND6	516006
MT-RNR1	561000
MT-RNR2	561010
MT-TA	590000
MT-TC	590020
MT-TD	590015
MT-TE	590025
MT-TF	590070

Gene Symbol	MIM #
MT-TG	590035
MT-TH	590040
MT-TI	590045
MT-TK	590060
MT-TL1	590050
MT-TL2	590055
MT-TM	590065
MT-TN	590010
MT-TP	590075
MT-TQ	590030
MT-TR	590005
MT-TS1	590080
MT-TS2	590085
MT-TT	590090
MT-TV	590105
MT-TW	590095
MT-TY	590100

Nuclear Genes Tested			
Gene	**MIM Number**	**Disorder**	**Inheritance**
ABCB7	300135	Sideroblastic anemia and ataxia	XL
ACAD9	611103	Mitochondrial complex I deficiency due to *ACAD9* deficiency	AR
ACADM	607008	Medium-chain acyl-CoA dehydrogenase (MCAD) deficiency	AR
ACADS	606885	Short-chain acyl-CoA dehydrogenase (SCAD) deficiency	AR
ACADVL	609575	Very long-chain acyl-CoA dehydrogenase (VLCAD) deficiency	AR
ACAT1	607809	Alpha-methylacetoacetic aciduria	AR
APTX	606350	Early-onset ataxia with oculomotor apraxia and hypoalbuminemia	AR
ASS1	603470	Citrullinemia type I	AR
ATPAF2	608918	Mitochondrial complex V (ATP synthase) deficiency, nuclear type 1	AR
BCKDHA	608348	Maple syrup urine disease type 1a	AR
BCKDHB	248611	Maple syrup urine disease type 1b	AR
BCS1L	603647	Mitochondrial complex III deficiency, nuclear type 1 Leigh syndrome	AR
COQ2	609825	Primary coenzyme q10 deficiency, 1	AR
COQ8A	606980	Primary coenzyme q10 deficiency, 4	AR
COQ9	612837	Primary coenzyme q10 deficiency, 5	AR
COX10	602125	Mitochondrial complex IV deficiency Leigh syndrome	AR

Gene	MIM Number	Disorder	Inheritance
COX15	603646	Leigh syndrome Cardioencephalomyopathy, fatal infantile, due to cytochrome C oxidase deficiency	AR
COX4I2	607976	Exocrine pancreatic insufficiency, dyserythropoietic anemia, and calvarial hyperostosis	AR
COX6B1	124089	Mitochondrial complex IV deficiency	AR
CPT1A	600528	Carnitine palmitoyltransferase deficiency, hepatic, type 1a	AR
CPT2	600650	Carnitine palmitoyltransferase deficiency, type II	AR
CYCS	123970	Thrombocytopenia 4	AD
DARS2	610956	Leukoencephalopathy with brainstem and spinal cord involvement and lactate elevation	AR
DBT	248610	Maple syrup urine disease type 2	AR
DGUOK	601465	Mitochondrial DNA depletion syndrome 3 (hepatocerebral type) Progressive external ophthalmoplegia with mitochondrial DNA deletions, 4	AR
DLAT	608770	Pyruvate dehydrogenase E2 deficiency	AR
DLD	238331	Dihydrolipoamide dehydrogenase deficiency	AR
DNAJC19	608977	3-methylglutaconic aciduria, type V	AR
DNM1L	603850	Optic atrophy 5 Encephalopathy due to defective mitochondrial and peroxisomal fission	AD
		Encephalopathy due to defective mitochondrial and peroxisomal fission	AR
ETFA	608053	Glutaric acidemia IIA	AR
ETFB	130410	Glutaric acidemia IIB	AR
ETFDH	231675	Glutaric acidemia IIC	AR
ETHE1	608451	Encephalopathy, ethylmalonic	AR
FASTKD2	612322	Mitochondrial complex IV deficiency	AR
FBXL4	605654	Mitochondrial DNA depletion syndrome 13 (encephalomyopathic type)	AR
FH	136850	Fumarase deficiency	AR
FOXRED1	613622	Mitochondrial complex I deficiency Leigh syndrome	AR
GFER	600924	Progressive mitochondrial myopathy with congenital cataract, hearing loss, and developmental delay	AR
GFM1	606639	Combined oxidative phosphorylation deficiency 1	AR
HADH	601609	3-hydroxyacyl-CoA dehydrogenase deficiency Hyperinsulinemic hypoglycemia, familial, 4	AR
HADHA	600890	Mitochondrial trifunctional protein deficiency Long-chain 3-hydroxyacyl-CoA dehydrogenase (LCHAD) deficiency	AR
HADHB	143450	Mitochondrial trifunctional protein deficiency	AR
HMGCL	613898	HMG-CoA lyase deficiency	AR
HMGCS2	600234	HMG-CoA synthase-2 deficiency	AR
HSPD1	118190	Spastic paraplegia 13	AD
		Hypomyelinating leukodystrophy, 4	AR
ISCU	611911	Hereditary myopathy with lactic acidosis	AR

Gene	MIM Number	Disorder	Inheritance
LARS2	604544	Perrault syndrome 4	AR
LRPPRC	607544	Leigh syndrome, French Canadian type	AR
MCCC2	609014	3-methylcrotonyl-CoA carboxylase 2 deficiency	AR
MFN2	608507	Hereditary motor and sensory neuropathy, type Via Charcot-Marie-Tooth disease, axonal, type 2A2A	AD
		Charcot-Marie-Tooth disease, axonal, type 2A2B	AR
MPV17	137960	Mitochondrial DNA depletion syndrome 6 (hepatocerebral type)	AR
MRPS16	609204	Combined oxidative phosphorylation deficiency 2	AR
MRPS22	605810	Combined oxidative phosphorylation deficiency 5	AR
NDUFA1	300078	Mitochondrial complex I deficiency	AR
NDUFA11	612638	Mitochondrial complex I deficiency	AR
NDUFA2	602137	Leigh syndrome due to mitochondrial complex I deficiency	AR
NDUFAF1	606934	Mitochondrial complex I deficiency	AR
NDUFAF2	609653	Mitochondrial complex I deficiency	AR
NDUFAF3	612911	Mitochondrial complex I deficiency	AR
NDUFAF4	611776	Mitochondrial complex I deficiency	AR
NDUFAF5	612360	Mitochondrial complex I deficiency	AR
NDUFS1	157655	Mitochondrial complex I deficiency	AR
NDUFS2	602985	Mitochondrial complex I deficiency	AR
NDUFS3	603846	Mitochondrial complex I deficiency Leigh syndrome	AR
NDUFS4	602694	Mitochondrial complex I deficiency Leigh syndrome	AR
NDUFS6	603848	Mitochondrial complex I deficiency	AR
NDUFS7	601825	Leigh syndrome	AR
NDUFS8	602141	Leigh syndrome	AR
NDUFV1	161015	Mitochondrial complex I deficiency	AR
NDUFV2	600532	Mitochondrial complex I deficiency	AR
NUBPL	613621	Mitochondrial complex I deficiency	AR
OPA1	605290	Optic atrophy 1 Optic atrophy plus syndrome	AD
		Behr syndrome	AR
OPA3	606580	Optic atrophy 3 with cataract	AD
		3-methylglutaconic aciduria, Type III	AR
OXCT1	601424	Succinyl-CoA:3-oxoacid-CoA transferase deficiency	AR
PC	608786	Pyruvate carboxylase deficiency	AR
PCK2	614095	Phosphoenolpyruvate carboxykinase deficiency, mitochondrial	AR
PDHA1	300502	Pyruvate dehydrogenase E1-alpha deficiency	XL

Gene	MIM Number	Disorder	Inheritance
PDHB	179060	Pyruvate dehydrogenase E1-beta deficiency	XL
PDHX	608769	Pyruvate dehydrogenase E3-binding protein deficiency	AR
PDP1	605993	Pyruvate dehydrogenase phosphatase deficiency	AR
PDSS1	607429	Coenzyme q10 deficiency, primary, 2	AR
PDSS2	610564	Coenzyme q10 deficiency, primary, 3	AR
POLG	174763	Progressive external ophthalmoplegia Mitochondrial DNA depletion syndrome 4a (Alpers type) or 4b (MNGIE type) Mitochondrial recessive ataxia syndrome (SANDO and scale)	AR
		Progressive external ophthalmoplegia	AD
POLG2	604983	Progressive external ophthalmoplegia with mitochondrial DNA deletions, 4	AD
PREPL	609557	Congential myasthenic syndrome, 22	AR
PUS1	608109	Myopathy, lactic acidosis, and sideroblastic anemia 1	AR
RARS2	611524	Pontocerebellar hypoplasia, type 6	AR
RRM2B	604712	Mitochondrial DNA depletion syndrome 8a or 8b	AR
		Progressive external ophthalmoplegia with mitochondrial DNA deletions, 5	AD
SCO1	603644	Mitochondrial complex IV deficiency	AR
SCO2	604272	Cardioencephalomyopathy, fatal infantile, due to cytochrome C oxidase deficiency 1	AR
SDHAF1	612848	Mitochondrial complex II deficiency	AR
SDHB	185470	Mitochondrial complex II deficiency	AR
SDHC	602413	Mitochondrial complex II deficiency	AR
SDHD	602690	Mitochondrial complex II deficiency	AR
SLC22A5	603377	Carnitine deficiency, systemic primary	AR
SLC25A13	603859	Citrullinemia, type II, adult-onset Citrullinemia, type II, neonatal-onset	AR
SLC25A15	603861	Hyperornithinemia-hyperammonemia-homocitrullinuria syndrome	AR
SLC25A19	606521	Microcephaly, Amish type Thiamine metabolism dysfunction syndrome 4	AR
SLC25A20	613698	Carnitine-acylcarnitine translocase deficiency	AR
SLC25A22	609302	Epileptic encephalopathy, early infantile, 3	AR
SLC25A3	600370	Mitochondrial phosphate carrier deficiency	AR
SLC25A4	103220	Mitochondrial DNA depletion syndrome 12a Progressive external ophthalmoplegia with mitochondrial DNA deletions 2	AD
		Mitochondrial DNA depletion syndrome 12b	AR
SLC3A1	104614	Cystinuria	AR
SPG7	602783	Spastic paraplegia 7	AR
SUCLA2	603921	Mitochondrial DNA depletion syndrome 5	AR
SUCLG1	611224	Mitochondrial DNA depletion syndrome 9	AR
SUOX	606887	Sulfite oxidase deficiency	AR

Gene	MIM Number	Disorder	Inheritance
SURF1	185620	Leigh syndrome due to COX IV deficiency Charcot-Marie-Tooth disease, type 4k	AR
TAZ	300394	Barth syndrome	XL
TIMM8A	300356	Mohr-Tranebjaerg syndrome	XL
TK2	188250	Mitochondrial DNA depletion syndrome 2 (myopathic type)	AR
TMEM70	612418	Mitochondrial complex v (ATP synthase) deficiency, nuclear type 2	AR
TRMU	610230	Liver failure, transient infantile	AR
TSFM	604723	Combined oxidative phosphorylation deficiency 3	AR
TUFM	602389	Combined oxidative phosphorylation deficiency 4	AR
TWNK	606075	Mitochondrial DNA depletion syndrome 7 (hepatocerebral type) Perrault syndrome 5	AR
		Progressive external ophthalmoplegia with mitochondrial DNA deletions, 3	AD
TYMP	131222	Mitochondrial DNA depletion syndrome 1 (MNGIE type)	AR
UQCRB	191330	Mitochondrial complex III deficiency, nuclear type 3	AR
UQCRQ	612080	Mitochondrial complex III deficiency, nuclear type 4	AR
WFS1	606201	Wolfram-like syndrome 1	AD
		Wolfram syndrome 1	AR

AD, autosomal dominant; AR, autosomal recessive; XL, X-linked

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RELATED INFORMATION

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Mitochondrial Diseases

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