Mitochondrial Disorders

Genetic Testing

Mitochondria are the powerhouse of the cell, providing energy from ATP production in the electron transport chain. Every cell contains hundreds to thousands of mitochondria, each with multiple copies of the mitochondrial genome. As cells are dividing to form the different tissues and organs in the body, mitochondria are divided randomly between daughter cells. For this reason, each tissue or organ in the body may have varying amounts of normal and variant mitochondrial DNA (mtDNA). This coexistence of normal and variant mtDNA is referred to as heteroplasmy. Disease can occur as the level of variant mtDNA, or heteroplasmy, increases. With increasing levels of variant mtDNA, symptoms may become more severe. Mitochondria are maternally inherited, and they are divided randomly when egg cells are produced during meiosis. Levels of heteroplasmy vary among family members as well as among tissues in an individual.

Greenwood Diagnostic Labs

Giving Greater Care

Clinical Information

Mitochondrial disorders represent a clinically heterogeneous group of conditions caused by pathogenic variants in either nuclear or mitochondrial DNA. Some mitochondrial disorders affect a single organ while most involve multiple organ systems. Mitochondrial disorders may present at any age and often include prominent neurologic and myopathic features. Mitochondrial disorders have variable penetrance and severity of symptoms depending on the level of mutant mitochondria, or heteroplasmy, within a given individual or tissue type.

Detection Rates for 29 Pathogenic Variants

Condition	Locus	Variant*	Clinical Detection Rate**
Hearing Loss ***	*MT-RNR1*	m.1494C>T	0.18-1.3%
Non-Syndromic Hearing Loss ***	*MT-RNR1*	m.1555A>G	0.3-11%
Leigh Syndrome	***MT-TL1***	**m.3243A>G**	<1%
	MT-TK	**m.8344A>G**	<1%
	MT-ATP6	**m.8993T>C**	~10-20%
		m.8993T>G	
		m.9176T>C	~1-5%
		m.9176T>G	~1-5%
		m.9185T>C	<1%
	MT-ND3	**m.10191T>C**	>1%
		m.10197G>A	>1%
	MT-ND4	m.11777C>A	<1%
	MT-ND5	**m.13513G>A**	~1-5%
		m.13514A>G	>1%
	MT-ND6	**m.14459G>A**	>1%
Leber Hereditary Optic Neuropathy	*MT-ND1*	m.3460G>A	95%
	MT-ND4	**m.11778G>A**	
	MT-ND6	m.14484T>C	
Maternally Inherited Diabetes & Deafness	*MT-TL1*	m.3243A>G	~2-7%
	MT-TS2	**m.12258C>A**	Unknown
Mitochondrial Encephalopathy, Lactic Acidosis, & Stroke-like Episodes	*MT-TL1*	**m.3243A>G**	~80%
		m.3271T>C	~7.5%
	MT-ND5	**m.13513G>A**	<10%
		m.13514A>G	<1%
Myoclonic Epilepsy & Ragged Red Fibers	*MT-TK*	**m.8344A>G**	~90%
		m.8356T>C	
		m.8363G>A	
Neurogenic Muscle Weakness, Ataxia, Retinitis Pigmentosa	***MT-TK***	**m.8993T>C**	~20-50%
		m.8993T>G	
	MT-ATP6	**m.9176T>C**	~1-5%
	MT-TV	**m.1606G>A**	<1%

*Variants in bold are associated with multiple mitochondrial conditions

**Clinical detection rate was taken from available literature. Contact the lab for specific sources.

***These variants are associated with Aminoglycoside-induced Deafness; however, the percentage provided is the portion of hearing loss and non-syndromic hearing loss accounted for by these variants.

Test	CPT Code(s)	Price
Common 29 mtDNA Variant Panel	81401x2, 81479	$1,400
Expanded 93 mtDNA Variant Panel	81401x2, 81479	$1,600
Targeted mtDNA Analysis: Known Familial Mutation (Sanger)	81403	$350
Targeted mtDNA Analysis with Heteroplasmy: Known Familial Mutation (NGS)	81403	$1,000

Detection Rates for 29 Pathogenic Variants

Condition	Locus	Variant*	Clinical Detection Rate**
Ataxia, Myoclonus, Mental Deterioration, and Deafness	***MT-TV***	**m.1606G<A**	Unknown
Ataxia Syndromes	***MT-ATP6***	**m.9185T>C**	Unknown
Cardiac & Multi-organ Dysfunction	***MT-TL1***	**m.3243A>G**	Unknown
Cardiomyopathy & Deafness	***MT-TK***	**m.8363G>A**	Unknown
Chronic Progressive External Ophthalmoplegia	*MT-TL2*	**m.3243A>G**	Unknown
		m.12315G<A	Unknown
Chronic Progressive External Ophthalmoplegia/ Mitochondrial Encephalomyopathy	*MT-TL2*	**m.12315G>A**	Unknown
Diabetes & Deafness/Retinitis Pigmentosa & Sensorineural Hearing Loss	*MT-TS2*	**m.12258C>A**	Unknown
Dystonia	***MT-ND3***	**m.10197G>A**	Unknown
Hypertrophic Cardiomyopathy	*MT-TI*	m.4300A>G	Unknown
Leber Hereditary Optic Neuropathy & Dystonia	*MT-ND3*	**m.10197G>A**	Unknown
	MT-ND6	m.14459G>A	Unknown
Mitochondrial Encephalopathy, Lactic Acidosis, & Stroke-like Episodes/Myoclonic Epilepsy & Ragged Red Fibers Overlap Syndrome	*MT-TH*	**m.12147G>A**	Unknown
Mitochondrial Myopathy with Maternally Inherited Diabetes and Deafness	*MT-TE*	**m.14709T>C**	Unknown
Progressive Encephalopathy	*MT-TG*	m.10010T>C	Unknown
Reversible COX Deficiency Myopathy	*MT-TE*	m.14674T>C	Unknown

Considerations for Testing

- Blood is the only accepted sample type for this assay.
- Mitochondrial variants can be missed if the level of variant mtDNA is not high enough in blood (see thresholds below).
- NGS can detect variants with a heteroplasmy of greater than 10%.
- Sanger sequencing (confirms variants from NGS) can detect variants with heteroplasmy greater than 20%.
- Variants with heteroplasmy levels below 20% Sanger sequencing threshold will be attempted to be confirmed by additional methods (for example, allele-specific PCR).
- Some mitochondrial variants are detectable in affected tissue but absent in blood, so these variants will not be identified in this assay.

Specimen Requirements: The required sample type is peripheral blood collected in an EDTA (purple top) tube - at least 2-3 ml for pediatric patients and 5-6ml for adult patients.

Transportation: The specimen should be kept at room temperature and delivered via overnight shipping. If shipment is delayed by one or two days, the specimen should be refrigerated and shipped at room temperature. Do not freeze the specimen. Samples collected on Friday can be safely designated for Monday delivery.

Expanded 93 mtDNA Variant Panel

Locus	Variants
MT-TF	**m.583G>A, m.616T>C**
MT-RNR1	**m.1494C>T, m.1555A>G**
MT-TV	**m.1606G>A**, **m.1630A>G, m.1644G>A**
MT-TL1	**m.3243A>G**, **m.3243A>T**, m.3256C>T, **m.3258T>C**, **m.3260A>G**, **m.3271T>C**, m.3273del, m.3280A>G, **m.3291T>C**, m.3302A>G, m.3303C>T
MT-ND1	m.3376G>A, **m.3460G>A**, m.3635G>A, m.3697G>A, m.3700G>A, m.3733G>A, m.3890G>A, m.3902_3908inv, **m.4171C>A**
MT-TI	**m.4298G>A**, **m.4300A>G**, m.4308G>A
MT-TQ	**m.4332G>A**
MT-TM	**m.4450G>A**
MT-TW	m.5521G>A, m.5537_5538insT
MT-TA	m.5650G>A
MT-TN	m.5690A>G, **m.5703G>A**, **m.5728T>C**
MT-CO1	m.7445A>G
MT-TS1 precursor	m.7445A>G
MT-TS1	m.7471dup, **m.7497G>A**, m.7510T>C, **m.7511T>C**
MT-TK	**m.8306T>C**, **m.8313G>A**, **m.8340G>A**, **m.8344A>G, m.8356T>C, m.8363G>A**
MT-ATP6/8	**m.8528T>C**
MT-ATP6	**m.8851T>C**, **m.8969G>A**, **m.8993T>G, m.8993T>C,** m.9035T>C, m.9155A>G, **m.9176T>G, m.9176T>C, m.9185T>C,** m.9205_9206del
MT-TG	m.10010T>C
MT-ND3	**m.10158T>C**, **m.10191T>C, m.10197G>A**
MT-ND4L	m.10663T>C
MT-ND4	**m.11777C>A, m.11778G>A**
MT-TH	**m.12147G>A**
MT-TS2	**m.12258C>A**
MT-TL2	m.12276G>A, **m.12294G>A**, **m.12315G>A**, m.12316G>A
MT-ND5	m.12706T>C, **m.13042G>A**, m.13051G>A, **m.13094T>C**, m.13379A>C, **m.13513G>A, m.13514A>G**
MT-ND6	**m.14459G>A**, m.14482C>G, m.14482C>A, **m.14484T>C**, **m.14487T>C**, m.14495A>G, m.14568C>T
MT-TE	**m.14674T>C, m.14709T>C,** m.14710G>A
MT-CYB	**m.14849T>C**, m.15579A>G

Variants in bold are associated with multiple mitochondrial conditions listed.

Familial & Follow-up Testing

Analysis for a familial variant is performed using either Sanger sequencing or Next Generation Sequencing (NGS). Sanger sequencing is only able to detect levels of heteroplasmy above 20% while NGS can detect levels as low as 10%. For this reason, Sanger sequencing may be considered as a first step in evaluating for the presence of a familial variant. NGS testing may be reserved for those who appear to be affected or who would be expected to carry the familial variant but have had negative Sanger sequencing results. As heteroplasmy levels vary from tissue to tissue, a negative blood test cannot completely rule out the chance that an individual carries the familial variant. Targeted maternal testing via Sanger sequencing is available at no charge following abnormal results in the proband.