

# Mitochondrial Genome (mtDNA) Disorders

**Disorder:** Mitochondrial disorders affect at least 1 in 5000 individuals and can be caused by mutations in either nuclear or mitochondrial genomes. Mitochondrial genome (mtDNA) is a 16.5 kb double-stranded circle of DNA containing 37 genes which are critical for mitochondrial function. The mutation spectrum in mtDNA can include point mutations, deletions and duplications, or complex rearrangements. The disorders caused by mtDNA mutations are heterogeneous and can be variable even between members of the same family. Disorders associated with mtDNA primarily affect high energy-demanding tissues such as nervous system and muscles, but multisystem involvement is not uncommon, particularly in pediatric patients.

mtDNA point mutations have been implicated in many disorders including:

- Mitochondrial encephalopathy with lactic acidosis and stroke-like episodes (MELAS)
- Myoclonic epilepsy with ragged-red fibers (MERRF)
- Leigh syndrome
- Neurogenic weakness with ataxia and retinitis pigmentosa (NARP)
- Leber hereditary optic neuropathy (LHON)
- Aminoglycoside-induced and nonsyndromic hearing loss

mtDNA deletions/duplications and rearrangements have been implicated in these additional disorders:

- Pearson marrow pancreas syndrome
- Kearns Sayre syndrome
- Sporadic progressive external ophthalmoplegia (PEO)

mtDNA disorders are maternally inherited. A mother with a mtDNA mutation will pass it on to all of her children, but only her daughters will pass it on to their children. A father with a mtDNA mutation will not transmit it to his children. Within a cell, there are often

thousands of copies of mtDNA, and heteroplasmy can be seen when mutated mtDNA coexists with non-mutated mtDNA in a cell. Variable amounts of heteroplasmy can be associated with differences in diseases. Large deletions and duplications are typically sporadic and not passed through families.

## Test Options:

- Whole mitochondrial genome (mtDNA) sequencing and deletion/duplication analysis by next-generation sequencing
- Whole mitochondrial genome (mtDNA) sequencing
- Common mutations mtDNA panel (mtDNA 1555, 3243, 3271, 3460, 8344, 8993, 11778, 14459, 14484)
- Neuromuscular disorders mtDNA panel (MELAS/ MERRF: mtDNA 3243, 3271, 8344)
- Leber Hereditary Optic Neuropathy mtDNA panel (mtDNA 3460, 11788, 14459, 14484)
- Hearing loss mtDNA panel (961, 1494, 1555, 3243, 3271, 7445, 7511, 8344)

\* See test requisition for reflex options

Additional information and test requisitions are available at: [www.cchmc.org/molecular-genetics](http://www.cchmc.org/molecular-genetics)

## Shipping Instructions:

Please enclose **test requisition** with sample.

**All information must be completed before sample can be processed.**

Place samples in styrofoam mailer and ship at room temperature by overnight Federal Express to arrive Monday through Friday

## Ship to:

Cytogenetics and Molecular Genetics Laboratories  
3333 Burnet Avenue NRB 1013  
Cincinnati, OH 45229  
513-636-4474

## Indications:

- Confirmation of diagnosis in a patient with physical manifestation of a mitochondrial disorder
- Presymptomatic diagnosis and/or carrier testing in a relative of a patient with a proven mtDNA mutation

## Specimen:

**Blood:** 3mL whole blood in purple top (EDTA) tube.

**Cytobrush (buccal sample):** 6 cytobrushes sent at ambient temperature. Please call for a free cytobrush collection kit.

**Tissue:** Minimum 30 mg. Samples must be flash frozen, and shipped on dry ice by overnight courier. Please call the laboratory prior to sending any tissue sample.

Label each item with patient's name, birth date, and date of collection.

**Testing Methodology:** Whole mitochondrial genome (mtDNA) sequencing and deletion/duplication analysis is amplified using long range PCR technology and followed by next-generation sequencing with > 1000 fold coverage at every target base. Mutation specific analyses and panels are performed by direct PCR-based sequence analysis of the specified mutations.

**Test Sensitivity:** Whole mitochondrial genome (mtDNA) is analyzed using long range PCR technology and followed by next-generation sequencing with > 1000 fold coverage at every target base. Mutation specific analyses and panels are performed by direct PCR-based sequence analysis of the specified mutations.

**Clinical Sensitivity:** Between 5-20% of patients with a suspected mitochondrial disease have an identifiable mtDNA mutation.

**Analytical Sensitivity:** The sensitivity of DNA sequencing is over 99% for the detection of nucleotide base changes, deletions and duplications in the regions analyzed. The current detection limit for heteroplasmic mtDNA by NGS sequencing is about 5%, and heteroplasmy level of all mutations is estimated. Although these analyses are very sensitive, a small possibility remains that a sequence alteration or deletion may go undetected due to technical errors or artifacts.

## Turn-Around Time:

- 28 days for mitochondrial genome sequencing
- 28 days for mitochondrial genome panels (Common mutations mtDNA panel, Neuromuscular disorders mtDNA panel, Leber hereditary optic neuropathy mtDNA panel, Hearing loss mtDNA panel)
- 28 days for mitochondrial genome deletion duplication analysis

## CPT Codes:

- mtDNA full genome sequencing: 81460
- mtDNA deletion/duplication analysis: 81465
- Common mutations mtDNA panel: 81401x8, 81479
- Neuromuscular disorders mtDNA panel: 81401x3
- Leber hereditary optic neuropathy mtDNA panel: 81401x3, 81479
- Hearing loss mtDNA panel: 81401(x3)
- Family specific mutation analysis: 81403

Please call 1-866-450-4198 for pricing, insurance preauthorization, or with any billing questions.

**Results:** Each test report includes a detailed interpretation of the genetic findings, the clinical significance of the result, and specific recommendations for clinical management and additional testing, if warranted. Results will be reported to the referring physician or health care provider as specified on the test requisition form.

## References:

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- Di Donato, S. (2009) J Neurol, 256(5), 693-710.*
- Huang, T., (2011) Curr Protoc Hum Genet, 2011. Chapter 19: p. Unit19 8.*
- Ingman, M. and Gyllenstein, U. (2006) Nucleic Acids Res, 34(Database issue), D749-51.*
- Schaefer, A. M. et al(2004) Biochim Biophys Acta, 1659(2-3), 115-20.*
- Tang, L.J. et al (2010) Biotechniques. 48(4): p. 287-96.*
- Wong, L. J. et al (2010) Mol Genet Metab, 100(2), 111-7.*