

# NATIONAL HEALTH LABORATORY SERVICE

**Inherited Metabolic Disease Laboratory**  
 Room 6.35 Falmouth Building, UCT Medical School, Observatory

Results NHLS call center tel: (021) 404 4129; IMD lab (021) 404 4449

## Mitochondrial DNA mutations screens

**Samples :-** *Leigh syndrome, LHON, NARP and Pearsons syndrome*

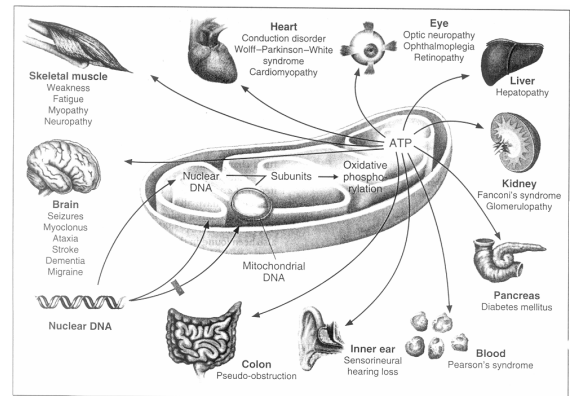
5ml EDTA blood – keep cool. **DO NOT FREEZE** .

**MERRF, MELAS, KSS and CPEO** . –

30mg muscle biopsy – Frozen (muscle preferred to blood to prevent false negatives (Pre-arrange with lab.)

**Leigh syndrome – enzyme assay** (Pre- arrange with lab.)

Skin biopsy – Please send in sterile container in either tissue culture medium of saline **DO NOT FREEZE**



### Request form.

Please clearly state the mutation screen required and/or the principle clinical symptoms.

If clinical symptoms do not clearly indicate one specific disease then all mitochondrial DNA mutations listed for Leigh, MERRF, MELAS and NARP syndrome will be screened (mitochondrial DNA screen). Further testing for Leigh's syndrome on request.

LHON, KSS, Pearson and CPEO are usually more clearly defined clinically and will be screened for by request.

### Leigh syndrome, MELAS, MERRF and NARP – request mitochondrial DNA screen if all 4 re quired

**Leigh Disease or Syndrome** - both genetic and enzyme assay is part of this screen

Long Name: Subacute Necrotizing Encephalomyelopathy. **Bilateral symmetric hypodensities in the basal ganglia is a characteristic feature.**

Symptoms: Seizures, hypotonia, fatigue, nystagmus, poor reflexes, eating & swallowing difficulties, breathing problems, poor motor function, ataxia.

Causes: Mutations in the multiple nuclear genes including :- **Pyruvate Dehydrogenase** complex (assayed by enzyme activity in fibroblasts, if deficient then subunit E1alpha sequenced – skin biopsy required), **Complex I, 11, 1V** (respiratory chain enzyme activity not assayed) and assembly proteins for complex 1V - SURF1 (gene sequenced).

Mitochondrial DNA point mutations **T9176C; G13513A; G14459A** account 10% of Leigh's cases

**MELAS** Long Name: Mitochondrial Encephalomyopathy Lactic Acidosis and Stroke-like Episodes.

Symptoms: Short stature, seizures, stroke-like episodes with focused neurological deficits, recurrent headaches, cognitive regression, disease progression, ragged-red fibers.

Cause: Mitochondrial DNA point mutations: **A3243G** (common); **T3271C; 3256T**

detect 80%-90% of MELAS cases

**MERRF** Long Name: Myoclonic Epilepsy and Ragged-Red Fiber Disease.

Symptoms: Myoclonus, epilepsy, progressive ataxia, muscle weakness and degeneration, deafness, and dementia.

Cause: Mitochondrial DNA point mutations: **A8344G; T8356C; G8363A**

detect 80%-90% of MERRF cases

**NARP** Long Name: Neuropathy, Ataxia, and Retinitis Pigmentosa

Symptoms: Late onset of peripheral neuropathy, ataxia, Retinitis Pigmentosa, basal ganglia lucencies.

Cause: Mitochondrial DNA point mutations in genes associated with Complex V: **T8993G; T8993C** detects 90% of NARP cases

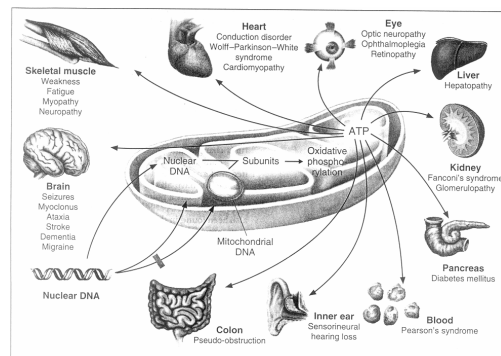
Common Clinical features	Leigh Syndrome	MELAS	MERRF	NARP
Maternal family history	+/-	+	+	+
Retinitis pigmentosa	-	-	-	+
Myoclonic seizures	-	-	+	+
Ataxia	+	-	+	+
Weakness	+	+	+	+
Seizures	+	+	+	+
Dementia	+	+	+	+
Short Stature	+	+	+	+
Sensorineural hearing loss	-	+	+	+
Neuropathy	+	+/-	+/-	+
Lactic acidosis	+/-	+	+	+/-
Ragged red fibers	+	+	+	+

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## Mitochondrial DNA mutations screens - continued

**LHON** Long Name: Leber Hereditary Optic Neuropathy.  
Symptoms: Primarily blindness in young men. Less common symptoms: mild dementia, ataxia, spasticity, peripheral neuropathy, and heart conduction defects.  
Cause: Mitochondrial DNA point mutations: **T14484C, G14459A; G11778A (common); G3460A; T9101C** detect 90% of LHON cases



### Mitochondrial DNA deletion syndromes

**CPEO** Long Name: Chronic progressive external ophthalmoplegia  
Symptoms: External ophthalmoplegia, bilateral ptosis, mild proximal myopathy, fatigue.  
Cause: Deletions of mtDNA in skeletal muscle

**KSS** Long Name: Kearns-Sayre syndrome  
Symptoms: External ophthalmoplegia, bilateral ptosis, mild proximal myopathy, diabetes mellitus, fatigue, hearing loss, seizures, cardiac conduction block, cerebellar ataxia, short stature, dementia, hypoparathyroidism. Renal tubular acidosis.  
Cause: Deletions of mtDNA in all tissue especially skeletal muscle

**Pearson's syndrome**  
Symptoms: Sideroblastic anemia, exocrine pancreatic dysfunction.  
Cause: Deletions of mtDNA in leukocytes.

### Rare mutations

Only the most common mutations associated with the diseases listed have been mentioned. All listed mutations have been found world wide in many different families and nationalities. Many hundred other point mutations and small deletions have been reported in mtDNA, however they are usually only associated with individual families and/or are region specific. The rare mutations account for less than 10% of all the reported cases. All mutations can be tested however due to financial restraints this is not recommended unless specific rare mutations are requested.

### COUNSELING ISSUES:

1. All children of a mother with a mitochondrial DNA mutation will inherit the mutation. However, clinical manifestations in the offspring depend on the degree of heteroplasmy (percentage of mutant vs. normal mitochondria) present in critical tissues. LHON and Leigh mutations are homoplasmic whereas MELAS, MERRF and NARP mutations are invariably heteroplasmic.
2. Testing of maternal relatives can confirm the presence of mutations but will not provide specific information regarding a prognosis. Clinical presentation can vary from normal to severe multisystem involvement due to the effects of heteroplasmy, mitotic segregation (random distribution of normal and mutant mitochondria into daughter cells during cell division) and threshold effects (percentage of mutant vs. normal mitochondrial DNA necessary to cause disease manifestations).
3. The absence of a discernable mitochondrial DNA mutations in the tissue tested does not rule out a disease diagnosis since the percentage of mutation will vary between tissues. Tissue with less than 10% of mutation is not detectible with a routine screen. Please note preferred tissue type for the different screens.
4. Counseling in LHON is further complicated by a higher frequency of affected males over females (approximately 4:1) suggesting the possibility of an X-linked susceptibility gene in addition to the mitochondrial mutation.
5. Mitochondrial DNA deletions are almost invariably not inherited (de novo). In addition deletions (varying sizes) in a very small percentage are often found in elderly people.

Contact tel: NHLS call center for all results: (021) 404 4129  
Laboratory: Surita Meldau (021) 404 4449  
Office: Dr Owen (021) 406 6219  
Tissue culture: Ingrid Baumgarten (021) 406 6102  
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