

Oxford Molecular Genetics Laboratory

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MITOCHONDRIAL DNA DISORDERS

including OMIM #530000, #557000, #540000, #545000, #551500, #256000, #520000, #580000

INTRODUCTION

Mitochondrial disorders are characterised by biochemical abnormalities of the respiratory chain, but are clinically and genetically heterogeneous. A subset of these disorders is due to defects in the mitochondrial DNA (mtDNA), which is present in multiple copies in the mitochondria and is maternally transmitted. MtDNA disorders include CPEO, Kearns-Sayre syndrome, Pearson syndrome, MELAS, MERRF, NARP, maternally-inherited Leigh syndrome, LHON (see separate page for further details), MIDD, aminoglycoside-induced deafness, and mtDNA depletion syndrome. Most of these disorders are maternally inherited or sporadic, however, mtDNA depletion syndrome and some forms of CPEO are autosomally inherited as a primary nuclear gene defect leads to secondary mtDNA defects. [We also provide a diagnostic service for a panel of these associated nuclear genes, and for reversible respiratory chain deficiency \(due to mtDNA mutation or TRMU mutation\)](#). The service is NHS Highly Specialised Services (HSS) funded for NHS referrals from England and Scotland (although the 3 common LHON mutations and pharmacogenetic testing for m.1555A>G are excluded from HSS funding).

TESTING

All samples **MUST** be accompanied by a completed Mitochondrial proforma ([click here](#))

Diagnostic:	Clinically affected patients
Carrier or Presymptomatic:	Relatives of clinically affected patients
Prenatal:	At risk of having an affected child

SAMPLE REQUIREMENTS

- Muscle or liver tissue (snap frozen and packaged on dry ice) is generally preferred. In particular, it is essential for all mtDNA depletion analysis and is recommended for mtDNA rearrangement analysis in individuals aged over 5 years. However, blood (5ml in EDTA, or 1-2ml for neonates) is adequate for most other analyses.
- For carrier/presymptomatic tests, other sample types may also be appropriate. Please contact the lab to discuss.
- Specific requirements for each sample type are available from the [Sample Requirements page](#).

REFERRALS

- From Hospital Consultants, mainly Clinical Genetics, Neurology, Paediatrics, Hepatology.
- Prenatal analysis is only undertaken in rare cases and must be arranged in advance. Prenatal referrals are only accepted from Clinical Genetics.

STRATEGY

- Genetic testing is directed by the clinical phenotype and the results of other investigations (e.g. biochemistry, tissue histology), and appropriate testing is reviewed locally.
- Analysis for specific mtDNA point mutations, mtDNA rearrangements and/or mtDNA depletion is undertaken as appropriate (also dependent on samples available).
- Where appropriate, this is followed by whole mtDNA next generation sequencing.

TECHNICAL INFORMATION

- Pyrosequencing or PCR & restriction digest for specific mtDNA point mutations (m.1555A>G, m.3243A>G, m.3260A>G, m.4300A>G, m.8344A>G, m.8993T>C/G, m.9176T>C, m.13513G>A, m.14459G>A, m.14674T>C/G & other mutations by special request)
- Long range PCR for mtDNA rearrangements, followed by Southern analysis to characterise single rearrangements detected
- Real-time PCR for mtDNA depletion (muscle or liver tissue/DNA required)
- Next generation sequencing (NGS) of the whole mitochondrial genome, by long-range PCR, Illumina NextEra library preparation and Illumina MiSeq sequencing.

TARGET REPORTING TIMES

Routine diagnostic tests (except mtDNA NGS):	28 calendar days
High priority diagnostic tests (except mtDNA NGS):	14 calendar days
Routine diagnostic mtDNA NGS:	112 calendar days
Pharmacogenetic test for m.1555A>G	14 calendar days
Carrier/Presymptomatic test:	14 calendar days
Prenatal testing (includes maternal contamination check):	3 calendar days