Oxford Molecular Genetics Laboratory

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AUTOSOMAL DISORDERS OF MITOCHONDRIAL DNA MAINTENANCE
including *POLG* related disorders

INTRODUCTION

Mutations in a number of genes have been associated with mitochondrial disorders in which disease pathology is due (at least in part) to defective mitochondrial DNA (mtDNA) maintenance. These mtDNA maintenance disorders are characterised by multiple mtDNA deletions and/or mtDNA depletion in post-mitotic affected tissues, such as muscle or liver. The following table lists the 21 genes for which a diagnostic service is provided and summarises the associated mitochondrial disease syndromes (MDS = mitochondrial DNA depletion syndrome):

Gene	Syndromes (inheritance pattern)
ABAT	Encephalomyopathic MDS (AR), GABA-aminotransferase deficiency (AR)
AFG3L2	PEO with spasticity/ataxia (AD)
AGK	Sengers syndrome (AR), Cardiomyopathic MDS (AR)
C10orf2 (PEO1)	PEO (AD), Hepatocerebral MDS (AR), IOSCA (AR)
DGUOK	Hepatocerebral MDS (AR)
DNA2	PEO (AD)
FBXL4	Encephalomyopathic MDS (AR)
MFN2	DOA+ (optic atrophy plus syndrome) (AD), MDS (AD)
MGME1	MDS (AR)
MPV17	Hepatocerebral MDS (AR), Navajo neurohepatopathy (AR), Neuropathy & leukoencephalopathy (AR)
OPA1	DOA (optic atrophy 1) (AD), DOA+ (optic atrophy plus syndrome) (AD)
POLG	Alpers / Hepatocerebral MDS (AR), PEO (AR/AD), SANDO (AR), MIRAS (AR), MNGIE-like (AR)
POLG2	PEO (AD)
RNASEH1	PEO (AR)
RRM2B	PEO (AD/AR), Encephalomyopathic MDS with renal tubulopathy (AR), MNGIE-like (AR)
SLC25A4(ANT1)	PEO (AD), Hypertrophic cardiomyopathy with myopathy & lactic acidosis (AR)
SPG7	PEO with spasticity/ataxia (AR, AD?)
SUCLA2	Encephalomyopathic MDS with methylmalonic aciduria (AR)
SUCLG1	Encephalomyopathic MDS with methylmalonic aciduria (AR)
TK2	Myopathic MDS (AR), PEO (AR)
TYMP	MNGIE (AR), MNGIE type MDS (AR)

We also offer a diagnostic service for mtDNA analysis, including deletion and depletion testing, and *TRMU* analysis.
The service is NHS Highly Specialised Services (HSS) funded for NHS referrals from England and Scotland.

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

REFERRALS

- From Hospital Consultants, mainly Clinical Genetics, Neurology, Paediatrics, Hepatology.
- Prenatal referrals are only accepted from Clinical Genetics and / or Prenatal Diagnosis. They must be discussed with the laboratory and arranged in advance.

STRATEGY

- Initial testing for 5 common autosomal recessive *POLG* mutations (if appropriate).
- Next generation sequencing (NGS) of the 21 genes listed above, in appropriate cases (usually when there is evidence of multiple mtDNA deletions or mtDNA depletion, or a dominant family history of PEO).
- Sanger sequencing of the following genes is also available as separate tests: *C10orf2, DGUOK, MPV17, OPA1, POLG, POLG2, RRM2B, SLC25A4, SUCLA2/SUCLG1, TK2.*
- For patients with infantile liver failure/dysfunction, *POLG*, *DGUOK* & *MPV17* can be sequenced alongside *TRMU*, by Sanger sequencing as a rapid test.
- Dosage analysis to test for exonic deletions/duplications as appropriate (not undertaken as part of the routine screens).

TECHNICAL INFORMATION

- Pyrosequencing for the common *POLG* p.Ala467Thr, p.Pro587Leu, p.Trp748Ser, p.Gly848Ser & p.Thr914Pro mutations (these mutations account for approximately 50-70% of autosomal recessive mutant alleles in populations of European origin).
- HaloPlex NGS for the panel of 19 genes. Libraries are sequenced on an Illumina MiSeq Desktop Sequencer. This will involve sequencing data generation in-house or by the High-Throughput Genomics Group at the Wellcome Trust Centre for Human Genetics, Oxford.
- Sanger sequencing of the entire coding region and exon-intron boundaries of the 11 genes listed under “Strategy” above.
- Dosage analysis by MLPA using kits P010 & P089 from MRC-Holland.

TARGET REPORTING TIMES

Urgent diagnostic tests for infants with acute liver failure under consideration for transplant:

7 calendar days	*POLG*, *DGUOK* & *MPV17* sequencing alongside *TRMU* sequencing

Routine diagnostic tests (high priority tests will be reported more quickly):

14 calendar days	*POLG* common mutation screen
112 calendar days	NGS panel of 21 genes
56 calendar days	Sanger sequencing of specific genes

Carrier/Presymptomatic tests:
14 calendar days

Prenatal testing (includes maternal contamination check): 3 calendar days

N.B. Details are correct for the date of printing only– last updated 14/07/2016