PIPADOR REVISION

MRCOG Part 1 Revision Notes

Mitochondrial Inheritance

GENETICS • LECTURE 79

VISUAL EXAMINATION REVISION NOTES

2026 Edition

MRCOG Part 1 Revision Notes

Lecture 79: Mitochondrial Inheritance

Genetics • Visual revision edition

COLOUR CODE USED THROUGHOUT THESE NOTES

NORMAL mtDNA	MUTANT mtDNA	NUCLEAR DNA	DONATION	CLINICAL

LEARNING OBJECTIVES — tick off as you go

- ☐ Describe the mitochondrial genome and why it is maternally inherited.
- ☐ Explain heteroplasmy, the bottleneck and the threshold effect.
- ☐ Recognise the classic syndromes and the clues to mitochondrial disease.
- ☐ Know that many mitochondrial diseases are nuclear-gene (Mendelian).
- ☐ Counsel on PGT, prenatal testing, mitochondrial donation, pregnancy and drug toxicity.

1 The Mitochondrial Genome

IN ONE LINE: *A 16.5 kb circle of 37 genes, present in hundreds to thousands of copies per cell — inherited only from the mother (sperm mitochondria are tagged and destroyed after fertilisation).*

The mitochondrial genome and key variants

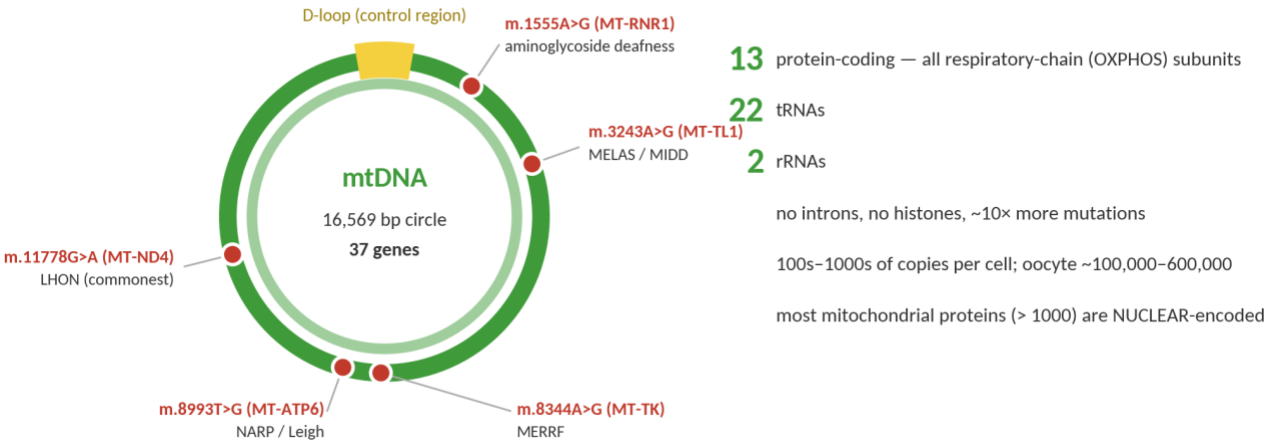


Figure 1. mtDNA and key variants.

2 Heteroplasmy, Bottleneck and Threshold

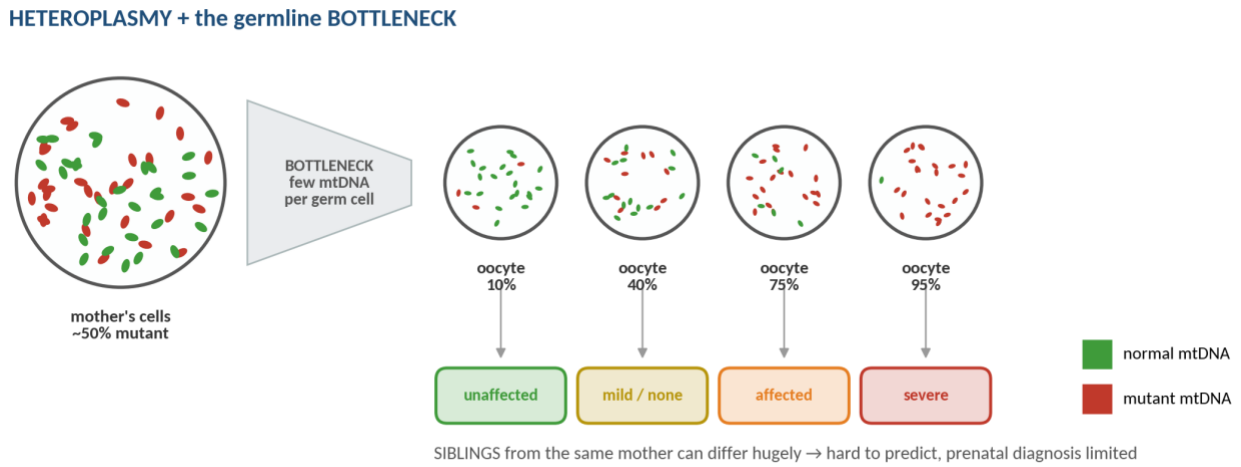


Figure 2. The bottleneck makes siblings differ.

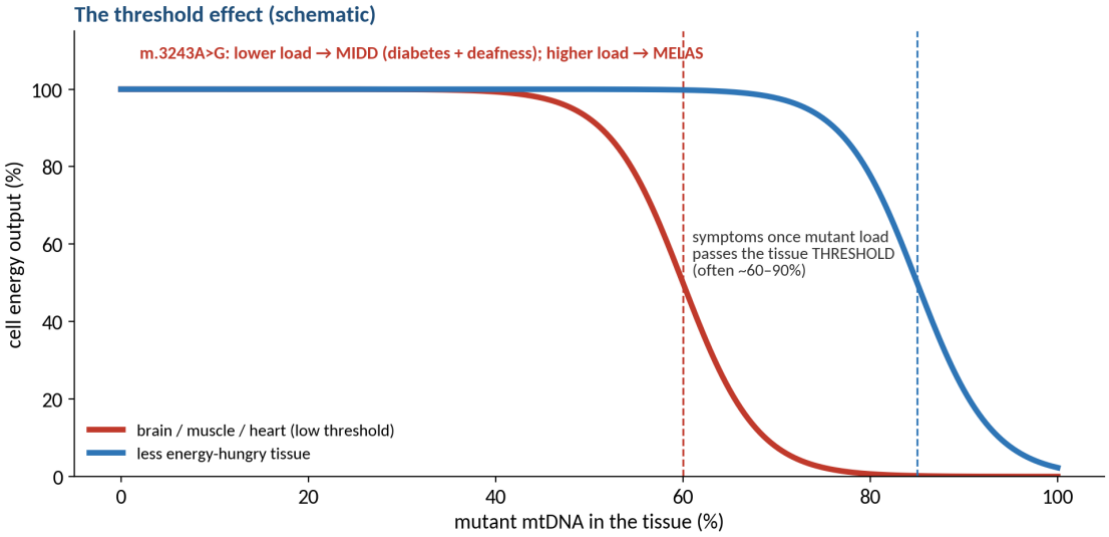


Figure 3. Threshold effect.

Term	Meaning
Homoplasmy	All copies the same (e.g. many LHON families)
Heteroplasmy	Mix of normal and mutant — the % varies between tissues, cells and over time
Bottleneck	Only a small number of mtDNA copies seed each oocyte → random big shifts in % between siblings
Threshold	Disease appears when mutant % passes a tissue-specific level (often ~60–90%) — energy-hungry tissues first

MNEMONIC / MEMORY HOOK

'Mum gives mitochondria — Dad gives nothing.' Mothers pass mtDNA to ALL children (how much varies); affected fathers pass it to NONE.

3 Mitochondrial Disease

- Affects ~1 in 5000. **Clues**: multisystem (brain + muscle + endocrine), maternal family pattern, **lactic acidosis**, raised CSF lactate. Tissues: brain (seizures, stroke-like episodes), muscle (myopathy,

ptosis/ophthalmoplegia), heart (cardiomyopathy, block), retina, cochlea, pancreas (diabetes), kidney (Fanconi).

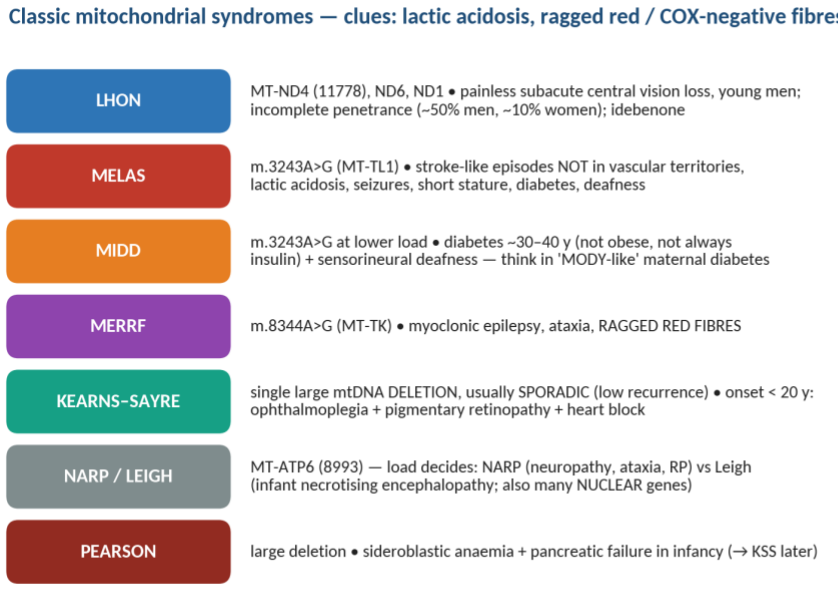


Figure 4. Classic syndromes.

- **Nuclear-gene mitochondrial disease** (> 1000 nuclear genes make mitochondrial proteins) follows **Mendelian** rules — e.g. **POLG** (mtDNA depletion; valproate → liver failure), many Leigh syndrome genes, Friedreich ataxia (frataxin, AR).

Test	Notes
Lactate / pyruvate	Blood and CSF
mtDNA testing	Blood can MISS variants (load falls in blood with age, esp. m.3243A>G) — urine or muscle better
Muscle biopsy	Ragged red fibres (Gomori trichrome), COX-negative fibres, respiratory-chain enzyme activity
MRI brain	Basal ganglia in Leigh; non-vascular stroke-like lesions in MELAS
Nuclear gene panel / exome	When mtDNA is normal

4 Reproductive Options

Mitochondrial donation — '3-parent IVF' (UK law 2015; HFEA licence 2017; first UK births reported 2025)

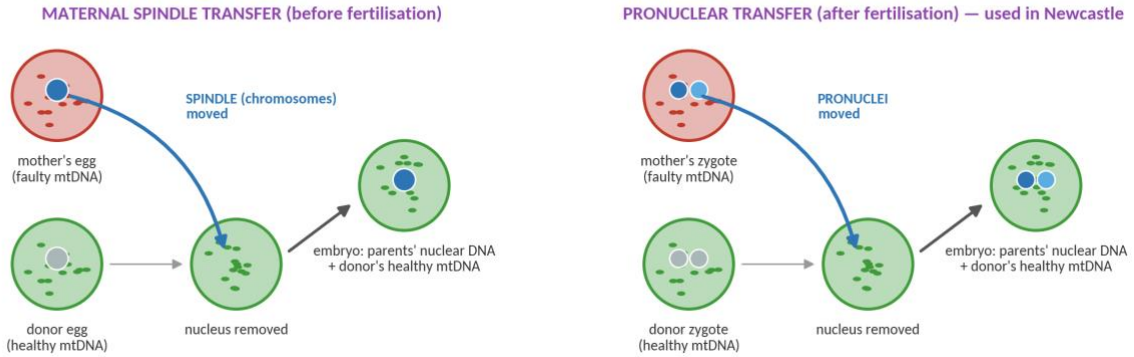


Figure 5. Mitochondrial donation.

PGT / PRENATAL TESTING

- **PGT**: pick embryos with LOW mutant load — reduces, doesn't remove, risk; useless if the mother's eggs are all high-load
- **Prenatal diagnosis** (CVS/amnio) limited: the % in a sample may not predict severity
- Egg donation or adoption are alternatives

MITOCHONDRIAL DONATION (UK)

- **Law passed 2015**; HFEA licensed Newcastle **2017** — case-by-case approval
- Spindle or **pronuclear transfer** (Newcastle) → baby with parents' nuclear DNA + donor mtDNA (< 0.1% of the genome)
- First UK births reported 2025; small risk of 'carry-over' of faulty mtDNA → follow-up

PREGNANCY IN A WOMAN WITH mtDNA DISEASE

- MDT: obstetrics, genetics, neurology, cardiology, anaesthesia
- Watch: diabetes, cardiomyopathy/arrhythmia, muscle weakness, seizures, lactic acidosis
- Avoid prolonged fasting, dehydration; caution with drugs that harm mitochondria

DRUGS + mtDNA

- **Aminoglycosides + m.1555A>G** → permanent deafness after one dose — bedside genetic tests now used on some neonatal units
- **Valproate** — avoid in POLG disease (liver failure)
- Older NRTI antiretrovirals, statins (myopathy)

★ PEARL

Same variant, different disease: m.3243A>G at low load → MIDD; high load → MELAS.

Kearns–Sayre deletions are usually sporadic — low recurrence, unlike point mutations.

5 MRCOG Exam Pearls — Last-Minute Page

Numbers to know

16,569 bp in mtDNA	**37** Genes (13 protein)	**~60–90%** Typical threshold	**~1 in 5000** Mito disease
3243 MELAS / MIDD	**1555** Aminoglycoside deafness	**2015 / 2017** UK law / first licence	**< 20 y** KSS onset

HIGH-YIELD CHECKLIST

- ☐ mtDNA: 16,569 bp, 37 genes (13 OXPHOS proteins, 22 tRNA, 2 rRNA).
- ☐ Maternal only; sperm mitochondria destroyed.
- ☐ Heteroplasmy + bottleneck → sibling variability; threshold effect.
- ☐ Clues: multisystem, lactic acidosis, ragged red / COX-negative fibres.
- ☐ LHON, MELAS, MIDD, MERRF, KSS, NARP/Leigh, Pearson.
- ☐ m.3243A>G: MIDD vs MELAS by load; blood may under-detect — use urine/muscle.
- ☐ Many 'mito' diseases are nuclear (POLG, Leigh genes) — Mendelian.
- ☐ PGT reduces risk; prenatal diagnosis limited.
- ☐ Mitochondrial donation: spindle or pronuclear transfer; Newcastle; HFEA.
- ☐ m.1555A>G + aminoglycosides; valproate + POLG.

Self-assessment — cover the right-hand column

Question	Answer
Why is mtDNA maternally inherited?	Sperm mitochondria are tagged (ubiquitin) and destroyed in the zygote
Define heteroplasmy.	Mix of normal and mutant mtDNA in a cell/tissue
Why do siblings vary so much?	The germline bottleneck
Variant behind MELAS and MIDD?	m.3243A>G (MT-TL1)
Classic muscle biopsy finding?	Ragged red fibres (and COX-negative fibres)
Which syndrome is usually a sporadic deletion?	Kearns–Sayre
Why is PGT limited for mtDNA disease?	It lowers but can't remove mutant load; % may not predict severity
Which transfer technique is used in Newcastle?	Pronuclear transfer
Variant causing aminoglycoside deafness?	m.1555A>G (MT-RNR1)
Drug to avoid in POLG disease?	Sodium valproate

6 References

- HFEA. Mitochondrial donation treatment — guidance and licensing.
- Gorman GS et al. Mitochondrial diseases. Nat Rev Dis Primers 2016.
- Turnpenny P, Ellard S. Emery's Elements of Medical Genetics. 16th ed. 2021.