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An Introduction to mitochondrial disease....

Dr Andy Schaefer

Consultant Neurologist and Clinical Lead
NHS Highly Specialised Rare Mitochondrial Disease Service and
Wellcome Trust Centre for Mitochondrial Research, Newcastle University,
Newcastle upon Tyne, UK

http://www.newcastle-mitochondria.com/
Mitochondrial Disease

Adult
- Single deletion

Neonatal
- Chronic progressive external ophthalmoplegia (CPEO)

Paediatrics
- MELAS syndrome
- MERRF
- Lebers hereditary optic neuropathy
- Chronic progressive external ophthalmoplegia (CPEO)
- POLG1

Clinical
- Maternally inherited diabetes and deafness
- Kearns-Sayre syndrome
- Leber's hereditary optic neuropathy
- SANDO
- NARP

Genetics
- mtDNA point mutation
- Multiple deletion
- Leigh's syndrome
- Mitochondrial depletion syndrome
Different Diseases

Photo via Creative Commons
Different Inheritance Patterns

- Sporadic
- X-linked
- Maternal
- Dominant
- Recessive
Different Patterns of organ involvement

Respiratory Failure

Optic Atrophy or Retinitis Pigmentosa

Cardiomyopathy

Stroke / Seizures Developmental delay

Liver Failure

Deafness

Short Stature

Peripheral Neuropathy

Marrow Failure

Diabetes

Thyroid Disease

Muscle weakness
Mitochondrial disease is **common** as a whole

Prevalence of **nuclear and mtDNA mutations** related to adult mitochondrial disease: 1 in 4300

UK-MRC Mitochondrial Disease Cohort (n=1395)

All have one thing in common

Energy Failure
Mitochondria turn fuel into energy
This doesn’t necessarily mean a global loss of energy – this occurs at a cellular level.
Best thought of like a country’s power grid – with local shortages affecting some areas more than others
This can lead to errors in susceptible organs
Multisystem disease
How is Mitochondrial Disease Inherited?

We’ll skip the first part…
Maternal Inheritance of mtDNA

Colours reflect inheritance of the same mitochondrial genome
Nucleus containing Chromosomes (99.9% of genetic Information - hair colour, blood group etc)

mtDNA disease

Mitochondria (batteries)

normal mtDNA

mutated mtDNA

(99.9% genetic Information - blood type, hair colour, etc.)
Nuclear genetic disorders: dominant and recessive inheritance

**Autosomal dominant**
- Affected father
- Unaffected mother

1 in 2 chance of affected child

**Autosomal recessive**
- Carrier father
- Carrier mother

1 in 4 chance of affected child

1 in 2 chance of affected daughter

1 in 2 chance of unaffected son

1 in 2 chance of unaffected daughter

1 in 2 chance of carrier son

1 in 2 chance of carrier daughter

1 in 2 chance of unaffected carrier son

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1 in 2 chance of affected affected affected affected son

1 in 2 chance of affected affected affected affected daughter
Nuclear DNA influence can create other inheritance patterns
The Quality Control analogy

Nuclear apparatus

Corrects Errors

Screens mtDNA
When quality control goes wrong

Abnormal mitochondrial DNA (and mitochondria) accumulate with time
Accumulation of mtDNA errors

Nucleus containing Chromosomes (99.9% of genetic Information - hair colour, blood type, etc)

Mitochondria (batteries)
So things are complicated...

Nuclear DNA disease

Inheritance:
- Dominant
- Recessive
- X-linked

Mt DNA disease

Inheritance:
- Maternal
PAEDIATRIC syndromes

- Barth syndrome
- PDH deficiency
- Alpers syndrome
- Pearson syndrome
- Leigh syndrome
- Kearns-Sayre syndrome
- MELAS

ADULT syndromes

- LHON
- MIDD
- MERRF
- NARP
- SANDO
- CPEO
- CPEO+
- MELAS

PAEDIATRIC syndromes
Nuclear DNA disease

Recessive
e.g. some forms of Leigh Disease

Each child has 1 in 4 chance of disease

Dominant

Each child has 1 in 2 chance of disease

- Red: disease
- Blue: unaffected
- Blue and red: Unaffected carrier
Mitochondrial DNA disease

Not ‘Yes’ or ‘No’?

But how much?

Nuclear: e.g. Dominant inheritance

Mitochondrial: Maternal inheritance
Less mitochondria – less energy

- Human Cell (the machine)
- Nucleus containing Chromosomes (blueprint)
- Mitochondria (batteries)
Average tissue levels can affect age of onset

- **Good mitochondria**
- **Bad mitochondria**

- Early muscle disease
- Late heart disease
- No brain disease
Variability associated with mtDNA mutation

“cell-to-cell”

“tissue-to-tissue”

“patient-to-patient”
Clinical relevance

Short stature/thin
Deafness
Cardiac problems
Seizures & stroke like events age 28

Asymptomatic when daughter presents
Deafness age 42
Weakness age 45
Off balance age 48

32% 56% 50%

Asymptomatic when sister presents and until retirement
Deafness age 64
Diabetes age 70

18% 22% 18%
Clinical relevance

Please note these are examples of potential clinical outcomes – they should not be used for purposes of genetic counselling as many factors affect prognosis. For personal or patient specific guidance a specialist in mitochondrial disease should be consulted.

- Short stature/thin
- Deafness
- Cardiac problems
- Seizures & stroke like events age 28: 83% (Red)

- Asymptomatic when sister presents and until retirement
  - Deafness age 64
  - Weakness age 45
  - Off balance age 48: 22% (Checkered)

- Asymptomatic when daughter presents
  - Deafness age 42
  - Weakness age 45
  - Off balance age 48: 18% (Red)

82% 68% 84%
18% 22% 18%
The effects of mutation loads (heteroplasmy)
Not everyone is qualified to give advice...
Important things to remember

Mitochondrial disease has no cure:
- But neither does asthma or diabetes and we look after those just fine.

We never used to have cures for pneumonia, congenital heart diseases or leukaemia
- But now we do.
Empathy
Passion
Expertise
Commitment
The future is bright...