

Mitochondrial DNA and genetic disease

Mitochondrial DNA (mtDNA) became news a few months ago when a publication in *Nature* announced that we may all be descended from a single African woman who lived 200 000 years ago.¹ The 'mitochondrial African Eve' hypothesis is based on the fact that mitochondria are strictly maternally inherited, and the accumulation of mutations can be used as a genetic clock.²

But mtDNA should not just remain the province of evolutionary biologists, feminists, and religious fundamentalists. To paediatricians it offers an explanation for maternal inheritance patterns in human disease, as an individual's mitochondria are inherited exclusively from the mother. For example, mitochondrial mutations could cause some types of mitochondrial myopathy,³ Leber's optic neuropathy,⁴ and could influence the clinical manifestations of congenital myotonic dystrophy⁵ and neurofibromatosis.⁶

The mitochondrial genome: 'small is beautiful'

Mitochondria are intracellular organelles which are key elements in oxidative phosphorylation. Their inner membrane binds the four complexes of the electron transport chain and adenosine triphosphate synthase (complexes I to V respectively). Mitochondria are the only source of extranuclear DNA in man, and each one contains two to 10 copies of a circular piece of DNA, which compactly encodes a minority of the RNAs and proteins the mitochondrion needs to function (figure).⁷ The billions of molecules of mtDNA in an individual are usually all identical, and inherited from the mother. This is presumably because the sperm contributes almost no cytoplasm to the zygote. A disease caused by a mutation in mtDNA would therefore be maternally inherited.

Characteristics to be expected of diseases caused by mitochondrial mutations

A disease caused by a mitochondrial mutation might have exclusively maternal transmission, a high proportion of offspring affected or transmitting the disease (compared with 50% in X linked disorders), and a biochemical defect in an enzyme with mitochondrially encoded subunits. (The absence of the latter point does not exclude a causative mitochondrial mutation. For example, in mice the

expression of a maternally transmitted antigen (MTA), is dependent on a variant mtDNA although the mechanism by which it interacts with this nuclear gene encoding the protein antigen is obscure.⁸) Likely human diseases include the mitochondrial myopathies, Leber's optic neuropathy, congenital myotonic dystrophy, and chloramphenicol induced aplastic anaemia. These criteria exclude a large number of conditions where nuclear encoded mitochondrial enzymes may be affected such as Leigh's encephalopathy, where inheritance is probably recessive.

A familiar alternative explanation for maternal inheritance is a transplacental biochemical factor, as occurs in transient neonatal myaesthesia gravis. Although this could explain the initial improvement in congenital myotonic dystrophy it does not explain the persistent developmental delay nor why non-myotonic offspring are unaffected, nor the progressive degeneration in Leber's and mitochondrial myopathy. While a biological transplacentally transmitted factor such as a slow virus could explain prolonged effects, there is no supporting epidemio-

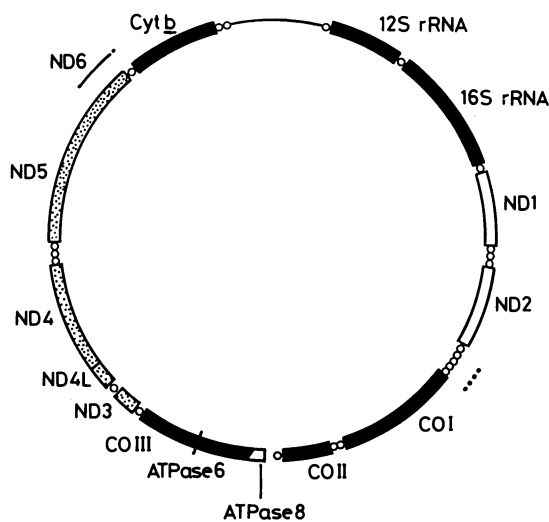


Figure The human mitochondrial genome. COI to COIII: subunits 1 to 3 of cytochrome C oxidase; ND1 to ND6, and ND4L: subunits 1 to 6 and 4L of NADH-dehydrogenase; ATPase 6 and 8: subunits 6 and 8 of H^+ -ATPase; Cyt b: apocytochrome B; O: transfer RNAs.

logical nor histological evidence. Alternatively, mitochondria might malfunction because of a nuclear mutation, causing male sterility due to the high energy requirements of the sperm. Finally, there is new evidence for 'imprinting' nuclear DNA according to its parent of origin.⁹

Mitochondrial myopathies

The mitochondrial myopathies are a heterogeneous group of rare disorders often associated with defects in the electron transport chain. They are characterised by abnormal mitochondria on muscle biopsy. However, clinical manifestations are not confined to skeletal muscle. Patients may present in the neonatal period with lactic acidosis, generalised weakness, and the Fanconi syndrome¹⁰ or later in childhood and early adult life with Kearns's Sayre syndrome,¹⁰ myoclonic epilepsy and ragged red fibres (MERRF),³ or mitochondrial encephalomyopathy lactic acidosis with stroke-like episodes (MELAS).¹¹ These clinical groups have limited nosological usefulness, however, as there is a range of disease and considerable variability even within a family.¹² Moreover, the biochemistry does not clearly parallel the clinical classification.¹³ Although most cases are sporadic, maternal inheritance is frequent in familial cases,^{13 14} and one large family with eight affected members has been described in which autosomal dominant and X linked inheritance was extremely improbable.³ While there are few families in which 100% of offspring are clearly affected, subclinical involvement has been described.³ It follows that mitochondrial mutations may well be causative in a proportion of these families.

Leber's optic neuropathy

Leber's optic neuropathy causes blindness with optic atrophy in adolescents and young adults,¹⁵ and should not be confused with Leber's amaurosis (retinal degeneration with visual loss in infants).¹⁶ It is exclusively maternally inherited, with a male:female ratio of 7:1 and around 80% of daughters becoming asymptomatic carriers.⁴ The biochemical basis is not well established, but some studies implicate rhodanese.¹⁷ Histology occasionally shows similarities with mitochondrial myopathy.^{18 19} It therefore partly fulfills the criteria for a mitochondrial disease, but if so, interactions of mitochondrial and nuclear gene products are involved (see discussion of mouse MTA above).

Congenital myotonic dystrophy

Myotonic dystrophy is an autosomal dominant

condition caused by a mutation on chromosome 19.²⁰ Although most cases present in adult life, around 10% are symptomatic in the neonatal period with hypotonia, poor suck, respiratory problems, and mental retardation. In these cases the mother is nearly always the affected parent.⁵ This could be explained by a transplacental factor. Alternatively some part of the mitochondrial genome could interact with the chromosome 19 defect, and the neonatal presentation occur only when both are present.

Chloramphenicol induced aplastic anaemia

Chloramphenicol is known to inhibit mitochondrial protein synthesis, and resistance is associated with a point mutation in the DNA coding for the 16s rRNA, the hypothetical binding site.²¹ A mutation in the binding site might predispose to chloramphenicol induced aplastic anaemia. Although pedigrees are consistent with maternal inheritance, however, familial cases are too rare for certainty.^{22 23}

Ways of looking for mitochondrial mutations

An altered mitochondrially encoded protein product, or more directly an analysis of the DNA itself could show a mitochondrial mutation. Most patients with mitochondrial myopathy appear to have normal mitochondrial proteins or a generalised reduction.²⁴ One case has been shown to have reduced levels of a single mitochondrially encoded peptide.²⁵

Gross alterations in mtDNA can be investigated by detection of restriction fragment length polymorphisms²⁶: subtle mutations such as single base changes, short insertions or deletions require DNA sequencing. So far, restriction mapping of patients with mitochondrial myopathy^{27 28} and Leber's optic neuropathy²⁹ has not shown any such major DNA changes in DNA from white cells. A recent unconfirmed report, however, suggests that there may be deletions of up to 7kb in muscle mtDNA in a proportion of patients with mitochondrial myopathy.³⁰

Thus far there is no published mtDNA sequence data for mitochondrial myopathy, Leber's optic neuropathy or myotonic dystrophy, although work is currently in progress. Sequence data on one patient with chloramphenicol induced aplastic anaemia shows a point mutation which could interact with chloramphenicol binding.²³ As this is present in a higher proportion of the normal population than are sensitive to chloramphenicol induced aplasia, its importance is uncertain.

Conclusion

Maternally inherited diseases could be caused by mutations in the mitochondrial genome. Some of the mitochondrial myopathies are probably examples of this, and perhaps Leber's optic neuropathy and susceptibility to chloramphenicol induced aplastic anaemia. Other diseases whose phenotype is affected by the parent from whom the abnormal gene originates could be caused by an interaction of abnormal mitochondrial and nuclear gene products. Clarification of these questions will aid genetic counselling, might enable non-invasive diagnosis, and allow therapeutic possibilities.

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