Dr. Anand Saggar
Medical Genetic Specialist

Mitochondrial disease

Mitochondrial diseases can be highly problematic. Mitochondrial disorders can be coded for by the nuclear genome. The incidence of mitochondrial respiratory chain diseases is

Under the age 6	=	1 in 1 000
Under age 16	=	1 in 21 000
Adults	=	1 in 8 000

Mitochondrial DNA (mtDNA) is a circular double stranded molecule encoding 37 genes, 13 of which encode components of the oxidative phosphorylation (OXPHOS) system. Typical cells can conatain up to 1000 mitohondria each with one or several copies of the mtDNA genome.

The organs most affected by mitochondrial diseases are those affecting high energy tissue such as the CNS, muscle, pancreas , liver and kidneys.

Terminology

- Homoplasmy is where there is only one type of mtDNA in the cell.
- Heteroplasmy where there are several different types of mtDNA either in the cell, organ or individual.
- Threshold effect is where abnormal mutational load above a threshold level,results in greatly impaired function and the severity of clinical symptoms increases sharply.
- Tissue variation is when the level of mutant mtDNA varies in different tissues.
- Selection is where there is preferential accumulation of mutant mtDNA load in certain tissues.

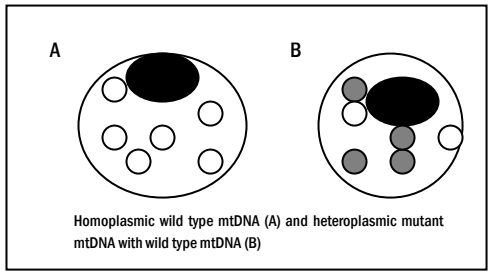
Mitochondrial inheritance

- The disorder can affect males and females equally
- MtDNA is almost exclusively maternally inherited
- Any paternal mitochondria entering at fertilization from sperm is later eliminated.
- Male to male transmission is possible but exceedingly rare.
- Mutation rates for mtDNA are 10-20 times that of nuclear DNA probably due to replication repair system errors
- Variable penetrance (frequency of developing the phenotype) and variable expression (severity of disease) are due to genetic and environmental modifiers.
- Point mutations are usually maternally inherited.
- Deletions and duplications are commonly sporadic occurrences.
- If a mother is heteroplasmic, the proportion of affected mtDNA in her offspring can vary greatly.

Figure
The mitochondrial Genome

Ragged red Fibres

Cartoon of homoplasmy and heteroplasmy



Homoplasmic wild type mtDNA (A) and heteroplasmic mutant mtDNA with wild type mtDNA (B)

Pictures:
Pic of mtDNA in cell
MtDNA genome
Ragged red fibres