# Oxidative phosphorylation diseases

*The clinical pathology may be caused by gene mutations in either mitochondri-al DNA (mtDNA) or nuclear DNA (nDNA) that encodes proteins required for normal OXPHOS.

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Ⓐ Mitochondrial DNA & oxidative phosphorylation Diseases:.

✔ The mtDNA is a small, 16569 nucleotide-pair, double stranded, circular DNA.... remember its evolution.

✔ It encodes 13 subunits of the complexes involved in OXPHOS:.

7 ⟶ complex 1

1 ⟶ complex III (3)

3 ⟶ complex IV (4)

2 ⟶ $F_o$ portion of ATP-synthase.

✔ mtDNA encodes the necessary components for translation of its mRNA: a large and small ribosomal RNA & tRNAs.

✔ The genetics of mutations in mtDNA are defined by maternal inheritance, replicative segregation, threshold expression, a high mtDNA mutation rate, & the accumulation of somatic mutations with age

➡ Replicative segregation when the mitochondria replicate by fission, the mutant or wild-type DNA are distributed to each daughter cell.

➡ heteroplasmy: when the cell have a mixture of mitochondria (mutant / wild-type DNA).

➡ somatic mutations result in a decline of oxidative phosphorylation capacity with age: accumulation of somatic mutations with age.

➡ Threshold expression: the ATP-generating capacity of a tissue falls below the tissue-specific threshold for normal function.

✔ In general, symptoms of these defects appear in one or more of the tissues with highest ATP demands: nervous tissue, heart, skeletal muscle and Kidney.

(Slide 1)

## (B) Other Genetic disorders of Oxidative phosphorylations.

✓ Most of the estimated 1,000 proteins required for oxidative phosphorylation are encoded by nDNA.

✓ Nuclear DNA mutations differ from mtDNA mutations in several important respects.....

These mutations don't show a pattern of maternal inheritance but are usually autosomal recessive.

✓ The mutations are uniformly distributed to daughter cells & therefore are expressed in all tissues that contain the allele for a particular tissue-specific isoform.

✓ However, phenotypic expression will still be most apparent in tissues with high ATP requirments.

(slide 2)