Unit II – Problem 2 – Genetics: Overview of Mitochondrial DNA Diseases

- **Mitochondria:**
  - They are intracellular organelles which are found in all cells except RBCs.
  - Notice that mitochondria has its own genome (mitochondrial genome: circular DNA molecule with no introns encoding for 37 genes only for protein synthesis). Notice that most proteins involved in mitochondrial metabolism and all those involved in mitochondrial DNA maintenance are nuclear encoded.

Mitochondrial component	Encoded by mitochondrial genome	Encoded by nuclear genome
Components of OXPHOS system	13 subunits	80 subunits
Components of protein synthesis apparatus	24 subunits	Approximately 80 subunits

Nuclear Genome vs. Mitochondrial Genome		
	Nuclear genome	**Mitochondrial genome**
Size	3200 Mb	16.6 kb
Number of different DNA molecules	23 pairs; all linear	One circular DNA molecule
Total number of DNA molecules per cell	46 in diploid cells	Often several thousands (but variable)
Associated protein	Several classes of histone & non-histone proteins	Largely free of protein (lack of histones)
Number of genes	35,000	37
Transcription	The great bulk of genes are transcribed individually	Co-transcription of multiple genes from both heavy and light strands
Introns	Found in most genes	Absent
% of coding DNA	1.5-3%	93%
Recombination	At least once for each pair of homologs at meiosis	No evidence for this occurring naturally
Inheritance	Mendelian for sequence on X and autosomes; paternal for sequence on Y	Exclusively maternal

  - **Function**: they are considered to be the major site for production of energy. Other functions include:
    - ✓ Production of Reactive Oxygen Species (ROS).
    - ✓ Programmed cell death (apoptosis).
    - ✓ Innate immune responses.

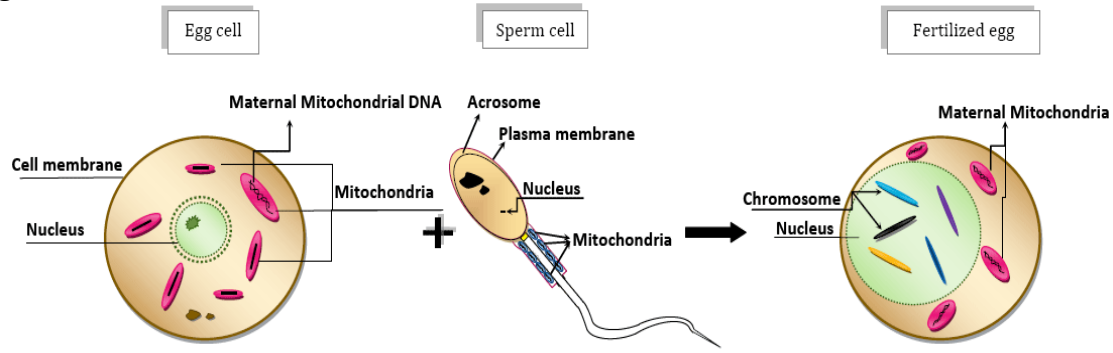
- **Mitochondrial diseases:**
  - They are clinically heterogenous group of disorders arising as a result of dysfunction of mitochondrial respiratory chain.
  - **Tissue affected in mitochondrial diseases:**
    - ✓ Heart: cardiomyopathy.
    - ✓ Eye: retinopathy.
    - ✓ Liver: hepatopathy.
    - ✓ Pancreas: diabetes mellitus.
    - ✓ Inner ear: sensory neural hearing loss.
    - ✓ Brain: seizures, stoke and dementia.
    - ✓ Skeletal muscles: weakness/fatigue and myopathy.

    Notice that symptoms mentioned above are common for most mitochondrial disorders.

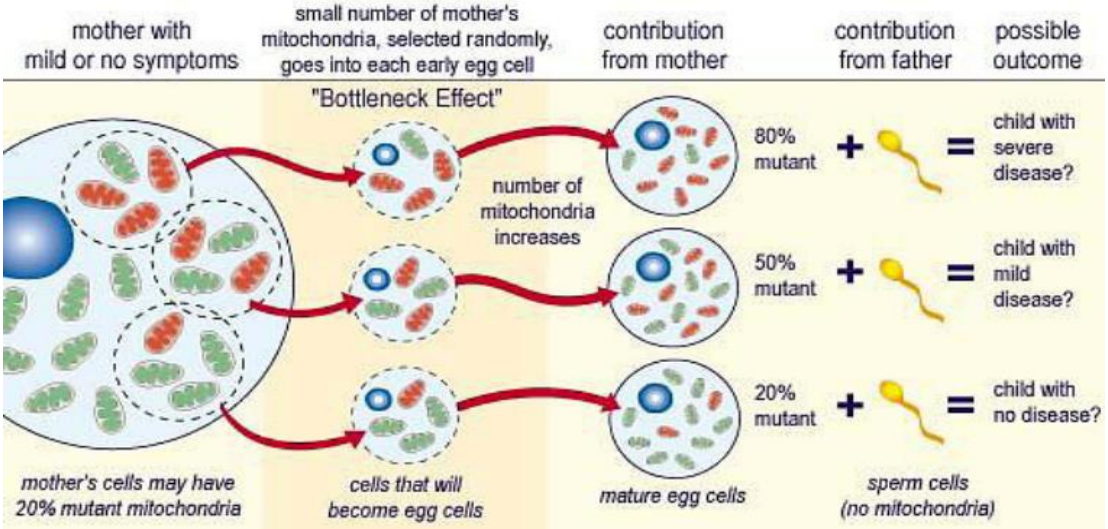
- **Types of mitochondrial diseases:**

Mitochondrial DNA defects	Inheritance is maternal and symptoms may be either more or less severe
Nuclear DNA defects	Inheritance is Mendelian
Random occurrence	Sporadic without affecting other family members (triggered by medications or other substances).

- **Mitochondrial inheritance:**
  - It is a maternal inheritance in which the mother transmits her mitochondrial genome to all her children but only the daughters will pass it on to all the members of the next generation and so on.



  - **Homoplasmy and heteroplasmy:**
    - ✓ Homoplasmy: completely normal or completely abnormal mitochondria within a cell.
    - ✓ Heteroplasmy: normal and abnormal mitochondria within a cell. When the mutated mitochondrial DNA exceeds a certain threshold it will be manifested in a pathogenic phenotype.
    - ✓ During cell division, three different genotypes can originate:
      - ❖ Homoplasmic normal mitochondrial DNA.
      - ❖ Homoplasmic mutated mitochondrial DNA.
      - ❖ Heteroplasmic mitochondrial DNA.
  - **Variations in inheritance of mitochondrial DNA mutations:**



  - **Genetic analysis of mitochondrial DNA mutations:**
    - ✓ Point mutation are detected by RFLP.
    - ✓ Deletions and duplication are detected by Southern Blot Hybridization.
    - ✓ Depletion detected by real-time PCR and Southern Blot Hybridization.