Mitochondrial Inheritance and Its Disorders

Course instructor: Jibril H. Yusuf PhD.

E-mail: jibril.habib@tiu.edu.iq

Course: Genetics II (MA 206)

Spring-Semester

Lecture 4

Date 16-08-2026

Outline

- What is Mitochondria
- Structure of mtDNA.
- Mitochondrial Inheritance
- Mitochondrial Disorders
- Characteristics of Mitochondrial Disorders
- Diagnosis of Mitochondrial Disorders

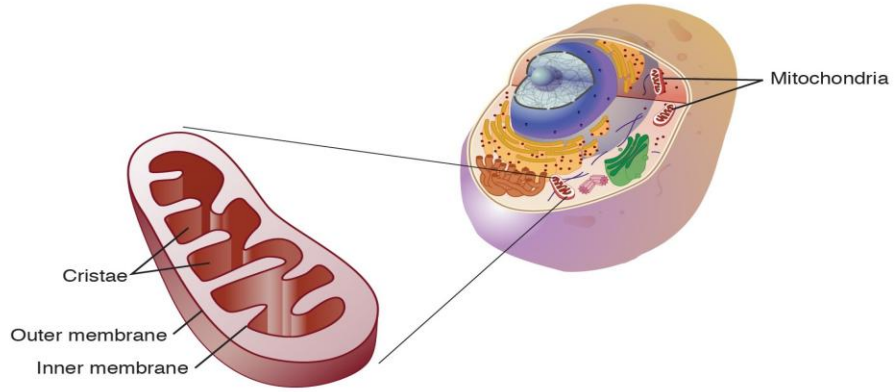
Objectives

- To understand and explain the fundamental principles of Mitochondrial Inheritance and Its Disorders.

❑ What is Mitochondria?

- Are essential organelles found in almost all **eukaryotic cells**, responsible **for producing adenosine triphosphate** (ATP) through **oxidative phosphorylation**.

- Mitochondrial DNA (**mtDNA**) has a unique **mode of inheritance** and is associated with specific **genetic disorders**.

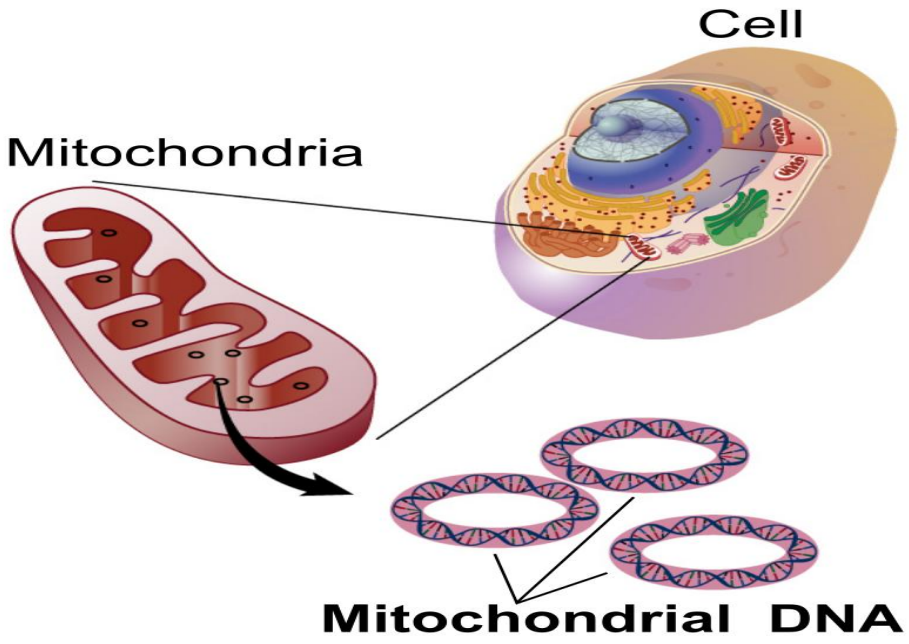


❖ Structure of mtDNA:

- **Structure**: mtDNA is a **circular**, **double-stranded** molecule.

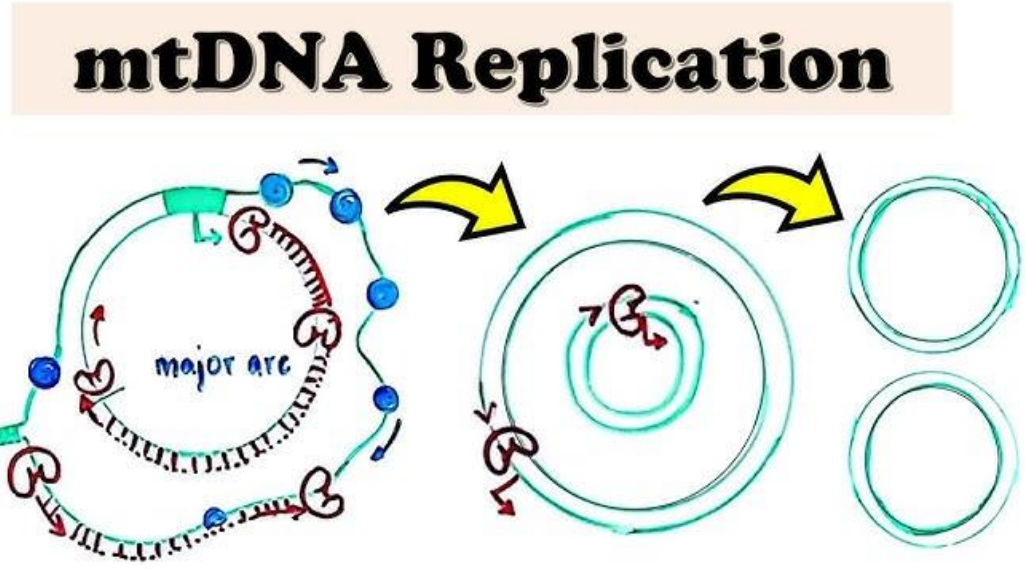
✓ It is much smaller than **nuclear DNA**, containing only **37 genes**.

✓ Encodes **13 proteins** for the electron transport chain, **22 tRNAs**, and **2 rRNAs**.



❑ mtDNA Replication and Transcription

- mtDNA replicates independently of nuclear DNA.
- It has a higher mutation rate **due to limited DNA repair mechanisms** and **exposure to reactive oxygen species** (ROS) generated during ATP production.

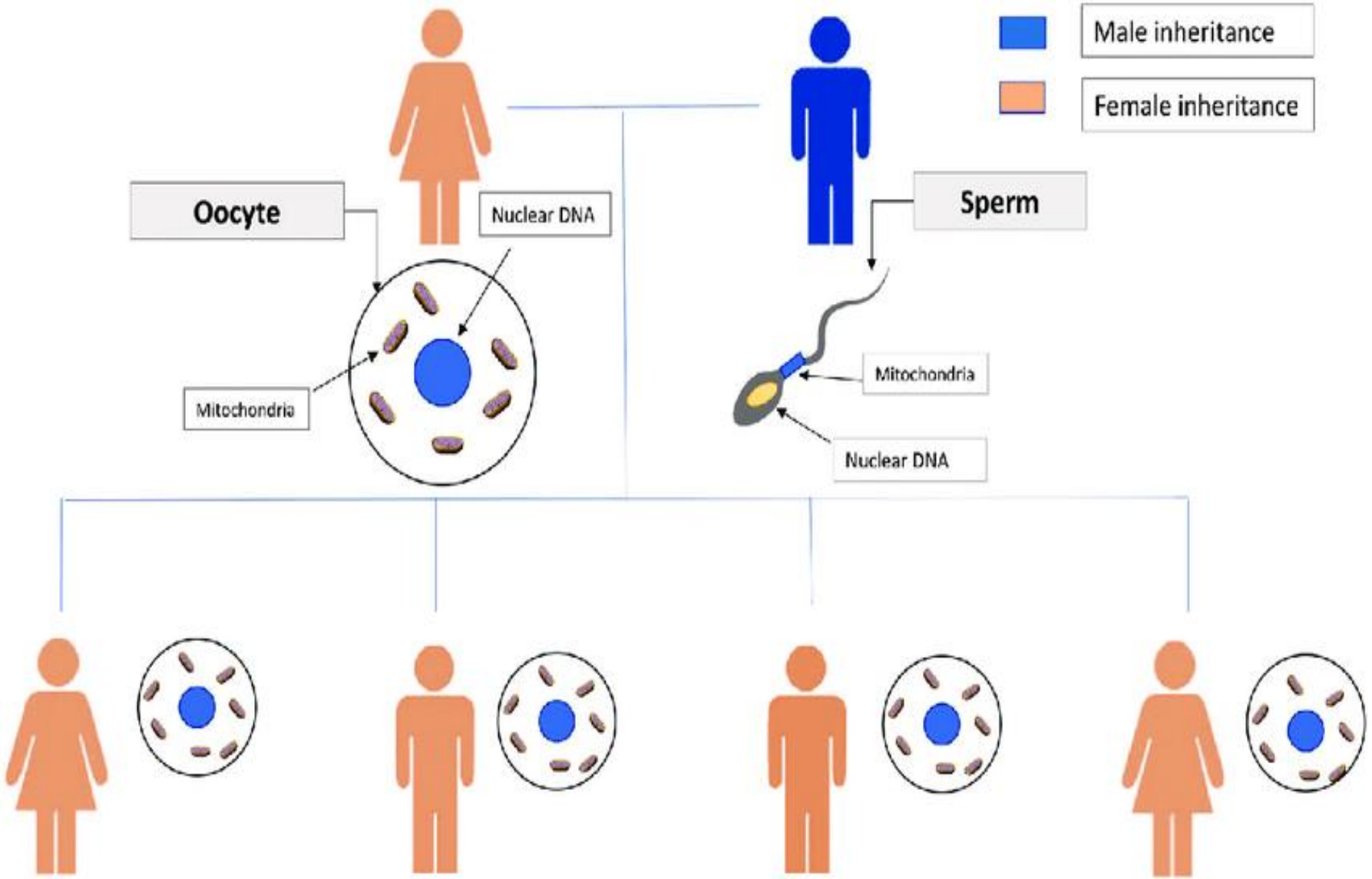


❑ Mitochondrial DNA Inheritance:

✓ Maternal Inheritance:

- ❖ Mitochondria are inherited exclusively from the mother.
- ❖ During fertilization, the sperm contributes nuclear DNA but not mtDNA, as sperm mitochondria are typically degraded.
- ❖ All offspring of an affected mother will inherit her mtDNA.

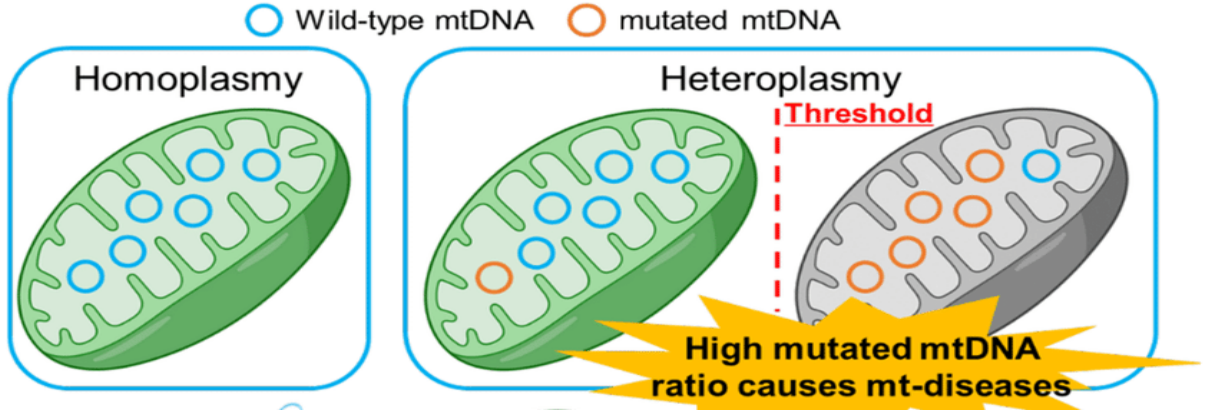
❖ Maternal Inheritance



❑ Heteroplasmy and Homoplasmy in mtDNA:

❖ mtDNA exists in multiple copies per cell, and variations in mtDNA can lead to two distinct states:

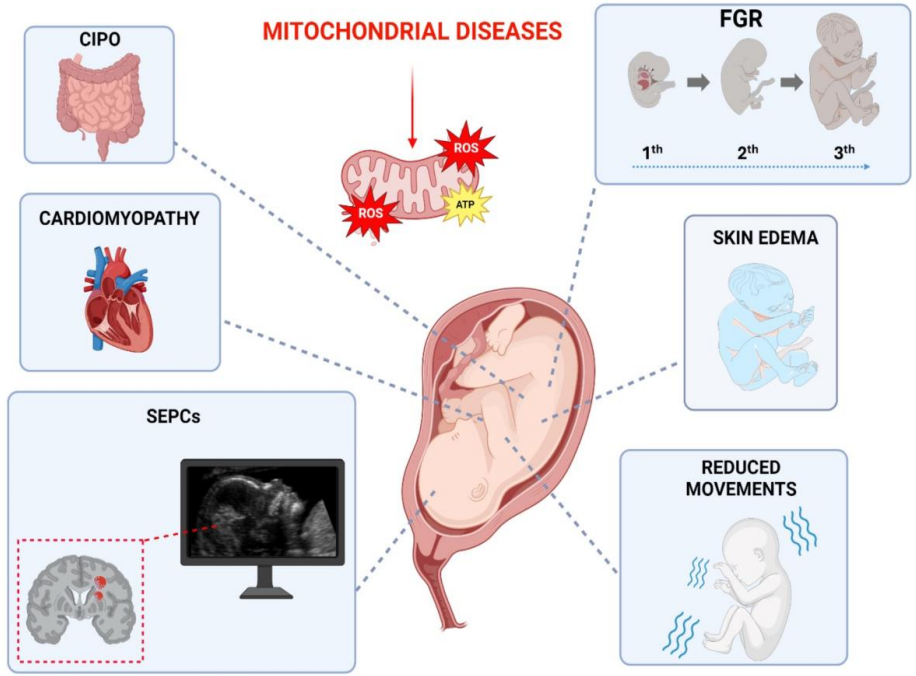
1. Homoplasmy: All mtDNA copies are identical (either normal or mutated.
2. Heteroplasmy: A mixture of normal and mutated mtDNA within a cell.



❑ Mitochondrial Disorders:

Definition: Are diverse group of conditions caused by defects in mitochondrial function.

These disorders primarily affect tissues with high energy demands, such as the brain, muscles, and heart.



❑ Characteristics of Mitochondrial Disorders

1. Multisystem involvement (neurological, muscular, cardiac, endocrine).

2. Variable expression due to heteroplasmy.

3. Progressive nature, often worsening over time.

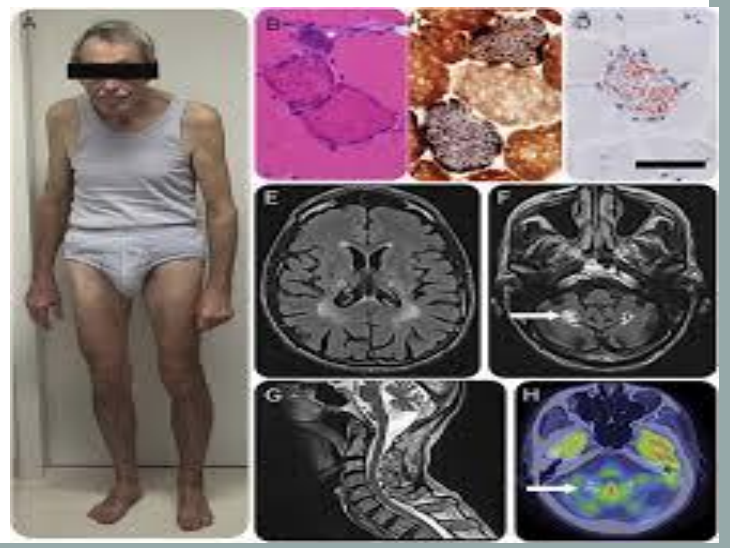
❑ Examples of Mitochondrial Disorders:

1. **Leber's Hereditary Optic Neuropathy (LHON):** Caused by mutations in mtDNA genes such as **m.11778G>A (MT-ND4).**

- **Symptoms:** Sudden **vision loss due to optic nerve degeneration**.
- The onset is usually **between 15–35 years**, but can occur at any age.
- Passed from the mother to offspring.

2. Mitochondrial Encephalomyopathy, Lactic Acidosis, and Stroke-like Episodes (MELAS):

- ✓ Caused by point mutations in mtDNA (e.g., **A3243G** in the tRNA leucine gene).
- **Symptoms:** Stroke-like episodes, seizures, muscle weakness, and lactic acidosis.
- Onset: Usually in early adulthood (2–40 years).
- Maternal inheritance

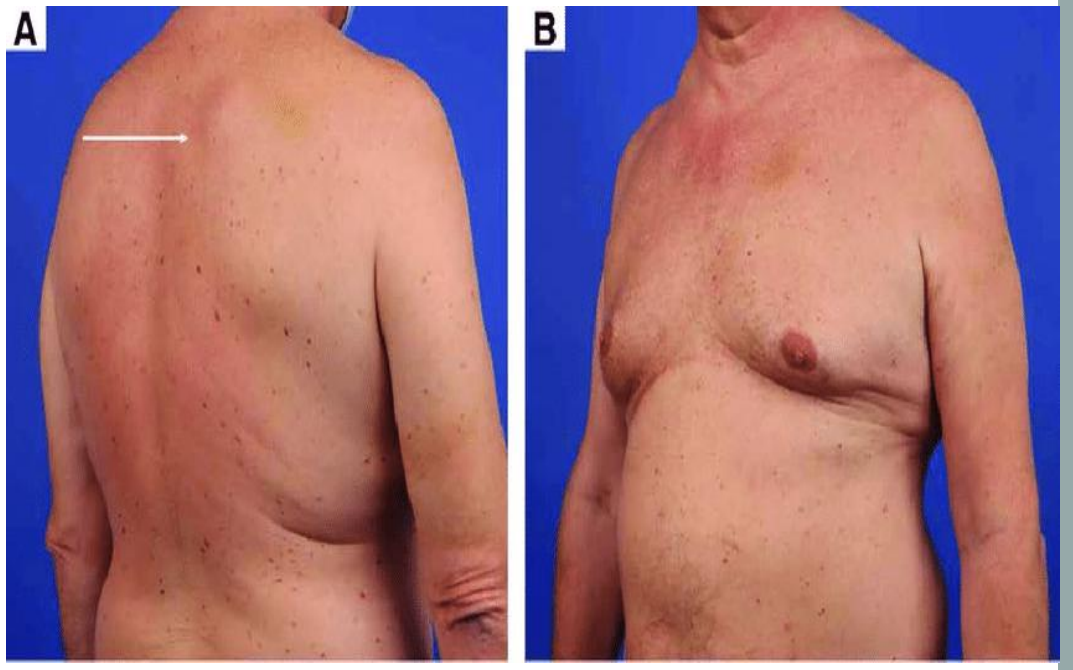


3. Myoclonic Epilepsy with Ragged Red Fibers (MERRF):

- ✓ Caused by mutations in the m.8344A>G (MT-TK tRNA lysine gene).

- Symptoms: Myoclonus (muscle jerks), epilepsy, ataxia, and ragged red fibers in muscle biopsies.

- Onset: Childhood to early adulthood.

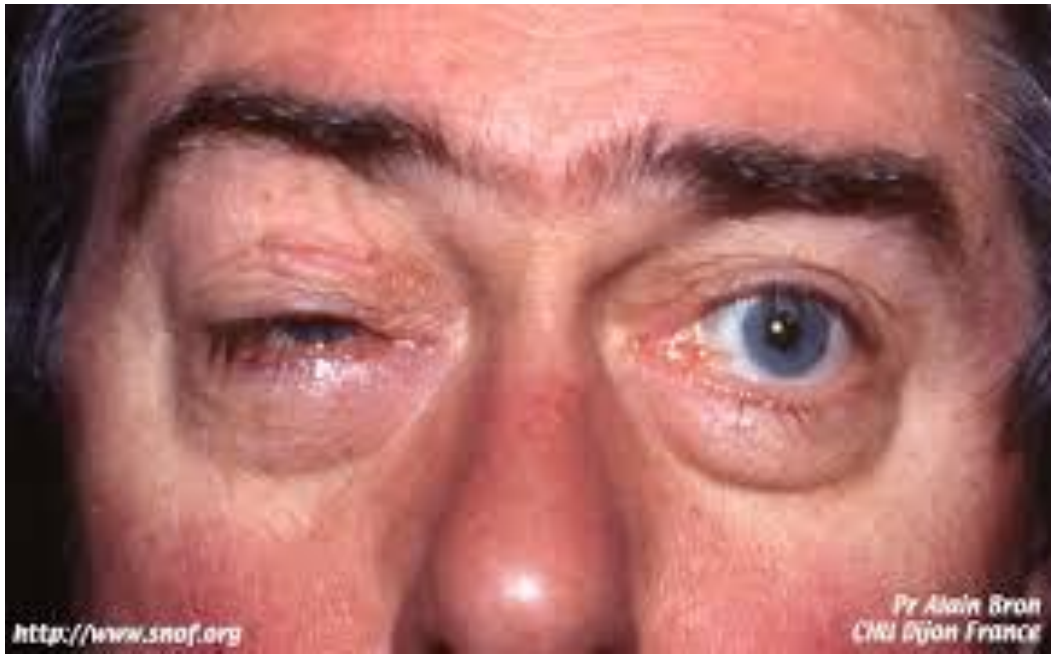


4. Kearns-Sayre Syndrome (KSS):

✓ Often caused by large-scale mtDNA deletions.

- Symptoms: Progressive external ophthalmoplegia, retinopathy, cardiac conduction defects, and ataxia.

- Onset: Before 20 years of age.



5. Leigh Syndrome:

- ✓ Caused by mutations in **MT-ATP**6 (mtDNA), affecting oxidative phosphorylation.

- Symptoms: Neurodegeneration, developmental delay, and lactic acidosis, typically presenting in infancy.

- Onset: Infancy before 2 years of age

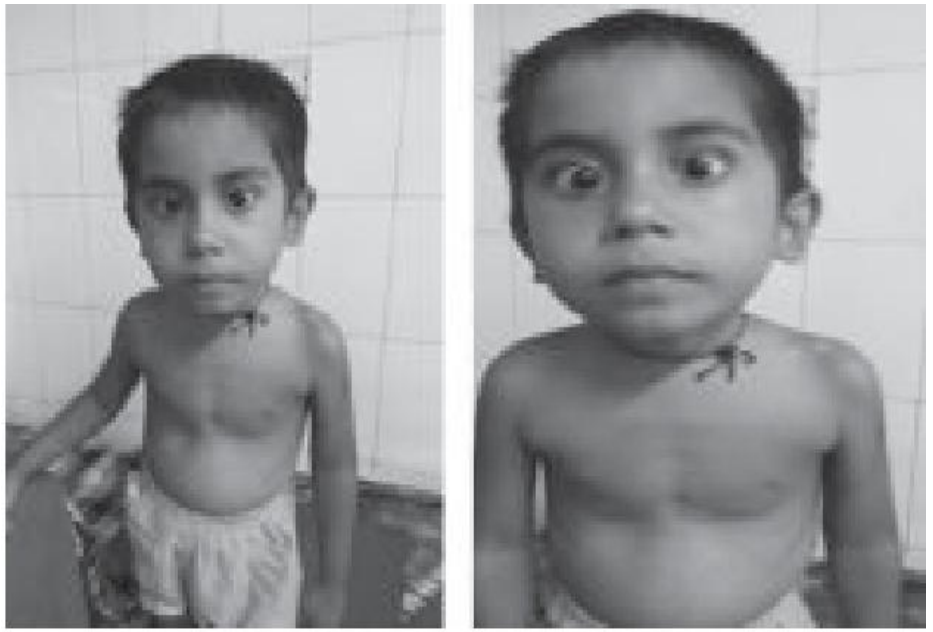


Figure 1&2: *showing bilateral convergent strabismus*

❑ Diagnosis of Mitochondrial Disorders

1. Clinical Evaluation:

- ✓ History, physical examination, and identification of multisystem involvement.

2. Laboratory Tests:

- ✓ Elevated lactate and pyruvate levels in blood or cerebrospinal fluid (CSF).

3. Genetic Testing:

- ✓ Sequencing of mtDNA to identify point mutations or deletions.

❑ Management and Treatment

A. **Supportive Care**:

- ✓ Physical therapy, occupational therapy, and speech therapy
- ✓ Management of seizures, diabetes, and cardiac complications.

B. **Nutritional Supplements**:

- ✓ Coenzyme Q10, creatine, and antioxidants (e.g., vitamin C, vitamin E).

C. **Experimental Therapies**:

- ✓ Gene therapy and mitochondrial replacement therapy (MRT) are under investigation.

❑ Genetic Counseling:

- ❖ Mitochondrial disorders have significant implications for family planning.
- ❖ Affected women have a 100% chance of passing mtDNA mutations to their offspring.
- ❖ Prenatal diagnosis and preimplantation genetic diagnosis (PGD) can help reduce the risk of transmission.

❖ Quiz:

Fill in the blanks

1. **Mitochondrial DNA is usually inherited from the _____.Answer: mother**
2. **Human mitochondrial DNA is approximately _____ base pairs long.Answer: 16,569**
3. **The presence of different types of mitochondrial DNA within a cell is called _____.Answer: heteroplasmy**
4. **Mitochondria are primarily responsible for producing cellular _____.Answer: energy (ATP)**
5. **Mitochondrial DNA is located only inside the nucleus.**
6. **Human mitochondrial DNA is circular.**
7. **A father normally transmits his mitochondrial DNA to all of his children.**
8. **Mitochondrial DNA contains 37 genes in humans.**
9. **Give two examples of mitochondrial disorders.**
10. **What is heteroplasmy?.**
11. **What is mitochondrial inheritance?**

References

1. Wallace DC. "Mitochondrial DNA mutations in disease and aging." Environmental and Molecular Mutagenesis, 2010.

2. DiMauro S, Schon EA. "Mitochondrial respiratory-chain diseases." The New England Journal of Medicine, 2003.

3. Vafai SB, Mootha VK. "Mitochondrial disorders as windows into an ancient organelle." Nature, 2012.

Thanks