

• الوراثة البشرية | المرحلة الثالثة - العام الدراسي ٢٠٢٠ -

٢٠٢١

• المحاضرة الثامنة | وراثة الميتاكوندريا -

## Mitochondrial Inheritance

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• وزارة التعليم العالي و البحث العلمي

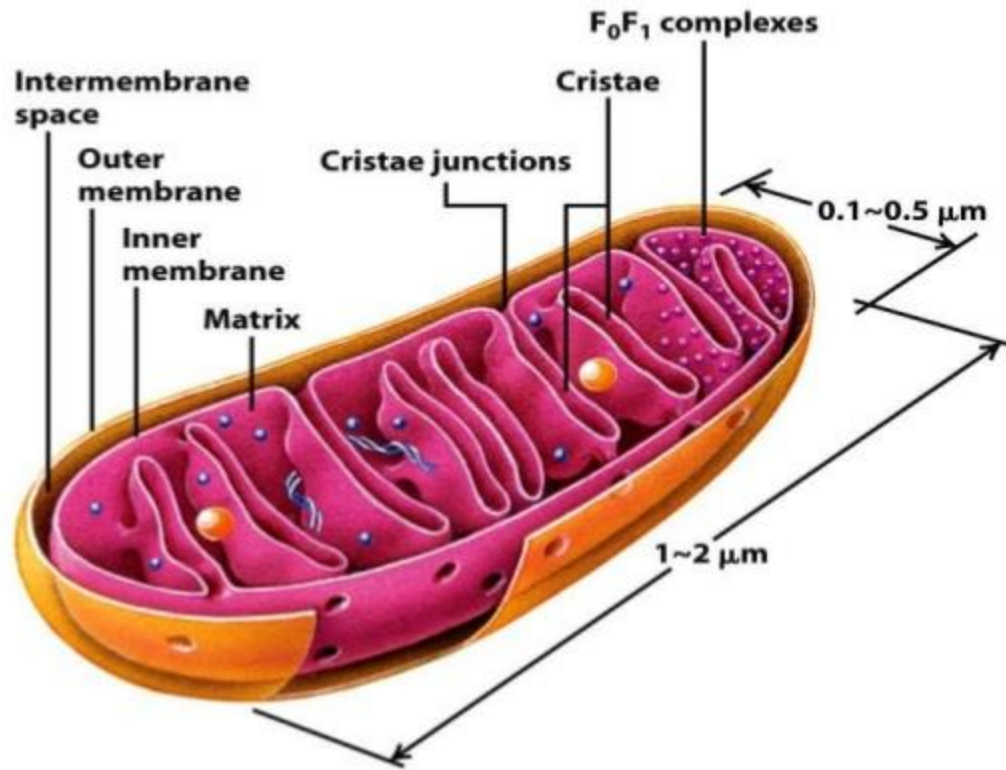
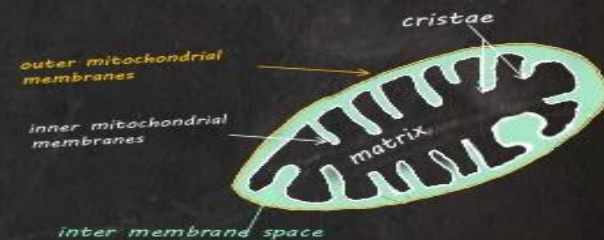


Figure 12-6a  
*Molecular Cell Biology, Sixth Edition*  
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## Characteristics of mitochondria DNA:

- Is inherited exclusively from the mother!  
*mtDNA* is a circular shape single chromosome
- It is only 16 kb in length - contains 16,600 bp.
- Codes for 37 genes.
- Contains 22 *tRNA* and 2 *rRNA* coding genes.
- Encodes 13 proteins that are subunits of oxidative phosphorylation.
- Contains only exons, no introns.
- Has no reparation system - high mutation rate especially in D-loop!
- No crossing over.
- Replicative segregation, homoplasmy & heteroplasmy



# CHARACTERISTICS

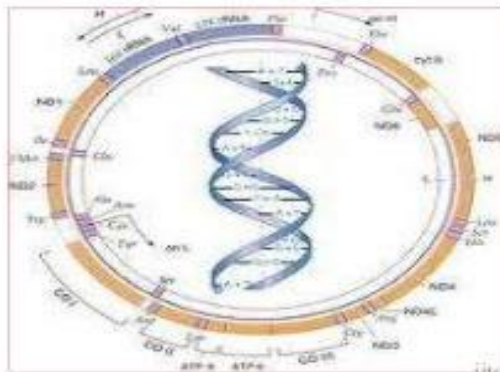
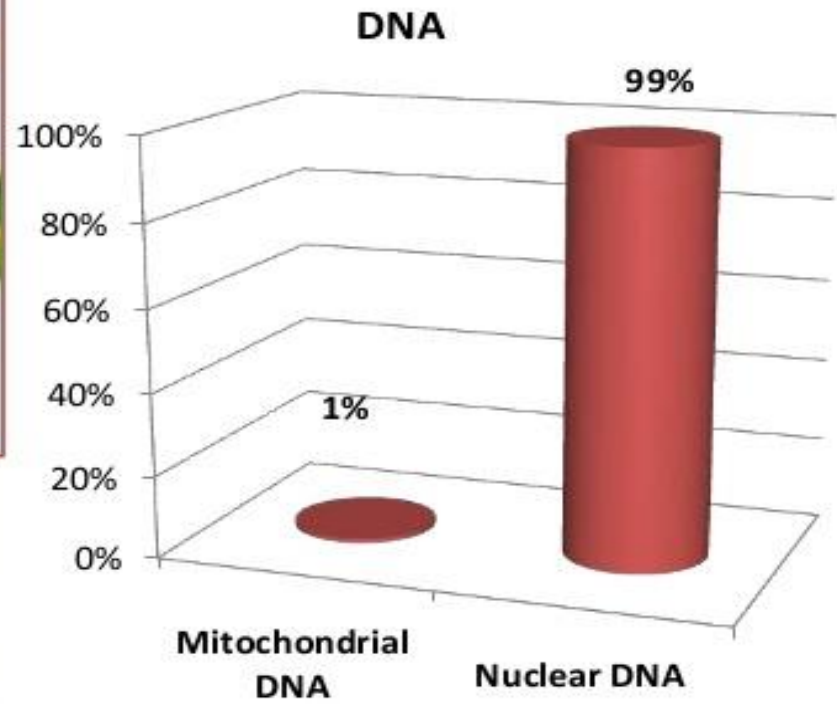
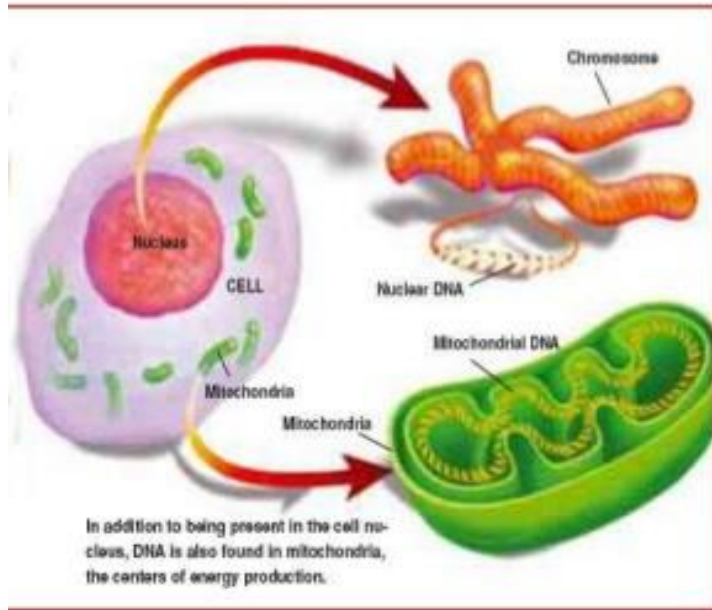
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## The Mitochondrial Genome

- **16,569** base pairs (**bp**) in length (16-18 kbp)
- encodes **37 genes**, **13 proteins**, **22 tRNAs**, and **2 rRNAs**

**two** general regions:

- **coding region**: responsible for the production of various biological molecules involved in "**cellular respiration**"
- **control region**: responsible for the **regulation of the mtDNA molecule**





## Nuclear DNA vs. Mitochondrial DNA

### ▶ Nuclear DNA

- ▶ found in **nucleus** of the cell
- ▶ 2 sets of **23 chromosomes**
- ▶ **maternal and paternal**
- ▶ can "**discriminate** between individuals of the same maternal lineage"
- ▶ **double helix**
- ▶ **bounded** by a nuclear envelope
- ▶ DNA **packed** into chromatin

### ▶ Mitochondrial DNA

- ▶ found in **mitochondria** of the cell
- ▶ each mitochondria may have **several copies** of the single mtDNA molecule
- ▶ **maternal only**
- ▶ **cannot "discriminate** between individuals of the same maternal lineage"
- ▶ **Circular**
- ▶ **free** of a nuclear envelope
- ▶ DNA is **not** packed into chromatin

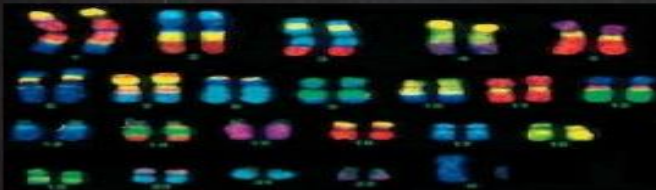
## Nuclear DNA vs. Mitochondrial DNA

### • Nuclear DNA

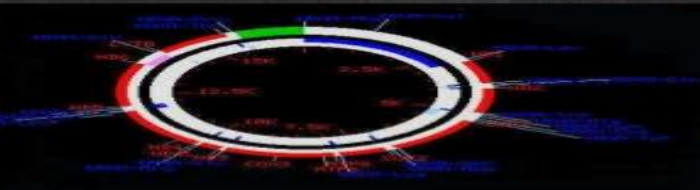
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- found in mitochondria of the cell
- each mitochondria may have several copies of the single mtDNA molecule
- maternal only
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**nucDNA genome**  
~3,000,000 Kbp  
>50,000 genes

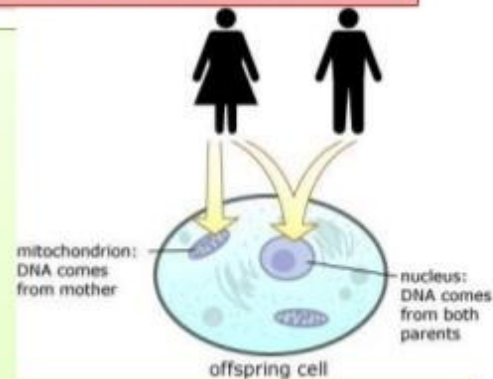


**mtDNA genome**  
≈17 Kbp  
38 genes



## Maternal Inheritance of mtDNA

During **fertilization**, the sperm only contributes its nucleus (**23 chromosomes**)



Mitochondria of the **sperm cell** are located at the mitochondrial sheath which is **destroyed** upon fertilization

Only available mitochondria (**mtDNA**) is that of the mother's; this is why mtDNA is of maternal origin

## Maternal Inheritance of mtDNA

- ▶ Sperm mitochondria are generally eliminated from the embryo so that mtDNA is inherited from the mother.
- ▶ All children of a female who is homoplasmic for a mtDNA mutation will inherit the mutation
- ▶ None of the offspring of a male carrying the same mutation will inherit the defective DNA
- ▶ Maternal inheritance of a homoplasmic mtDNA mutation causing **Leber Hereditary optic neuropathy** is known.

# MITOCHONDRIAL INHERITANCE

FATHER CARRYING  
MUTATED mtDNA

MOTHER NOT CARRYING  
MUTATED mtDNA



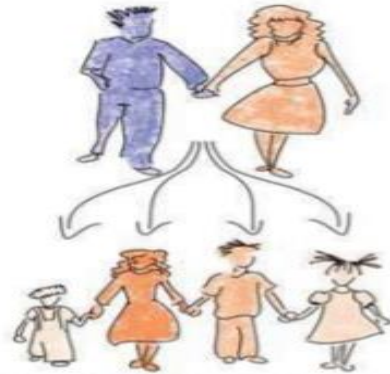
NO CHILD CARRIES MUTATED  
MITOCHONDRIA FROM THEIR  
FATHER

- OTHER CARRIERS WILL EXPERIENCE SYMPTOMS. THESE WILL AFFECT DIFFERENT TISSUES AND INDIVIDUALS WITH DIFFERENT SEVERITY AND CAN ONSET AT ANY AGE

- SOME CARRIERS OF MUTATED MITOCHONDRIAL DNA WILL EXPERIENCE MILD SYMPTOMS OR NONE, SO MIGHT NOT KNOW THEY ARE CARRIERS

FATHER NOT CARRYING  
MUTATED mtDNA

MOTHER CARRYING  
MUTATED mtDNA

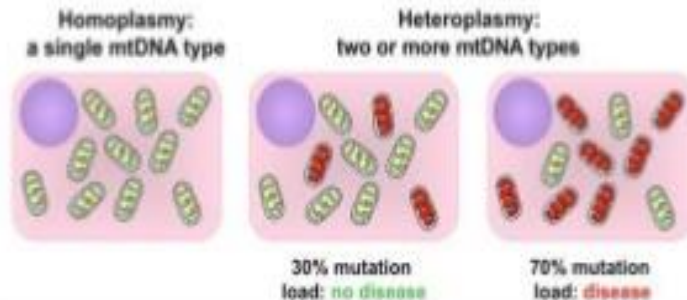


EVERY CHILD CARRIES MUTATED  
MITOCHONDRIA FROM THEIR MOTHER,  
AND WILL BE VARIABLY AFFECTED

# Homoplasmy and Heteroplasmy

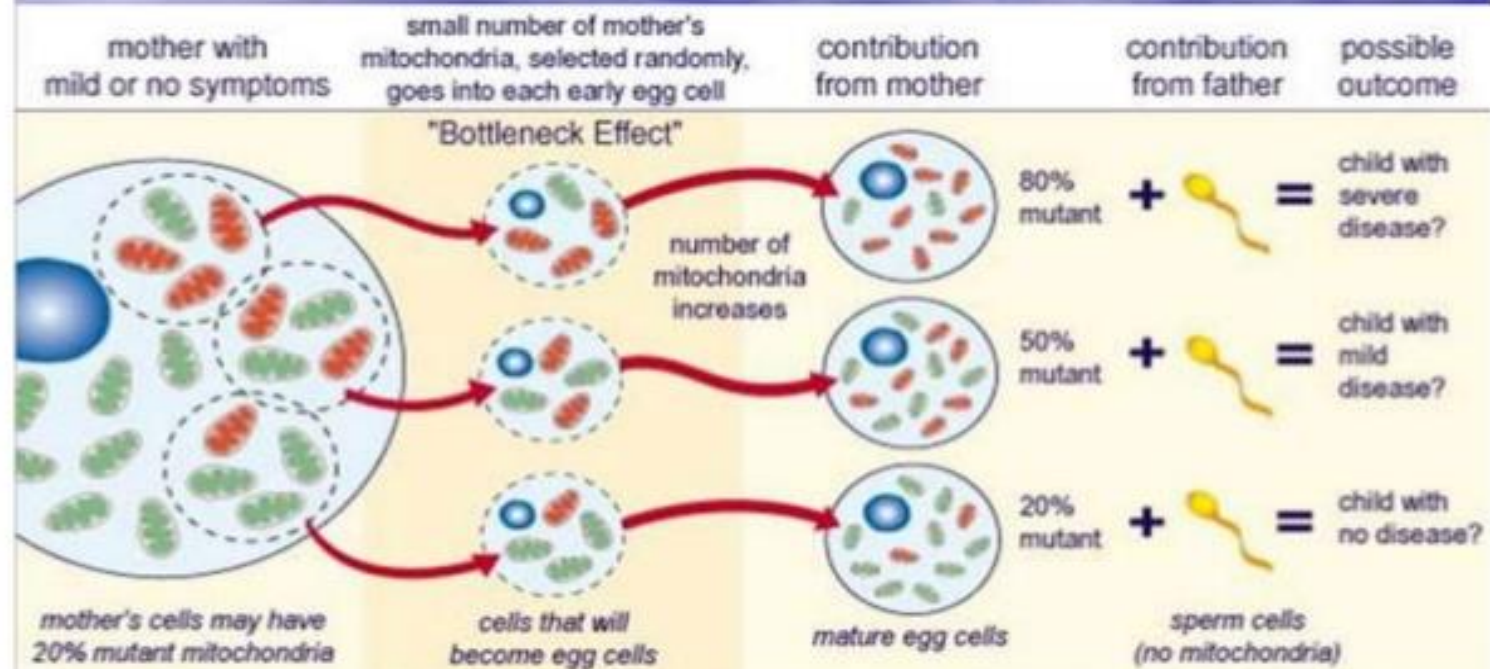
- ▶ One daughter cell may by chance receive mitochondria that contain only a pure population of normal mtDNA or a pure population of mutant mtDNA (**Homoplasmy**)
- ▶ The daughter cell may receive a mixture of mitochondria some with and some without mutation (**Heteroplasmy**)

In normal conditions mtDNA is **HOMOPLASMIC**  
Many pathogenic mutations are **HETEROPLASMIC**





# MATERNAL INHERITANCE OF MITOCHONDRIAL DNA MUTATIONS



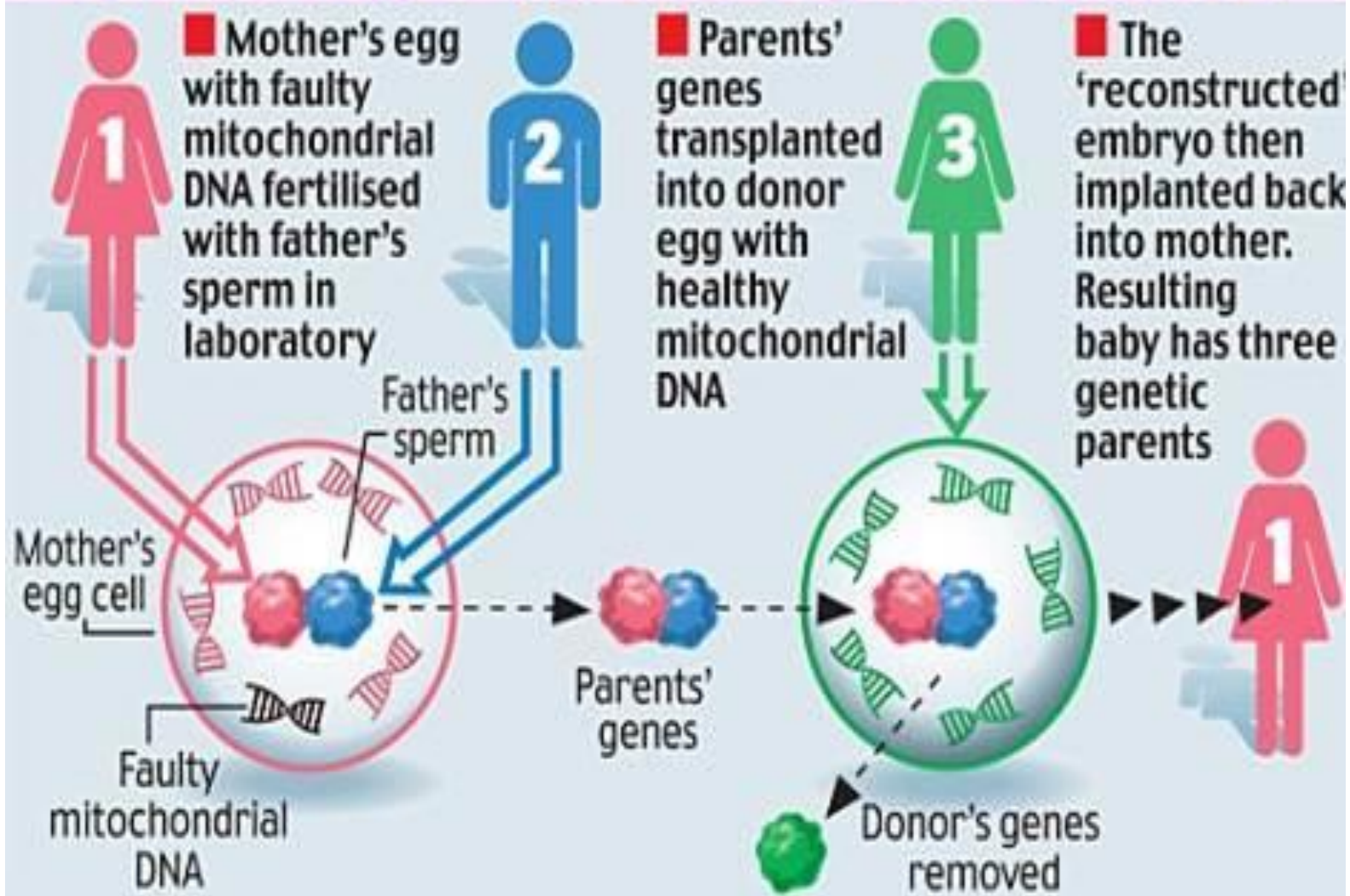
**MITOCHONDRIAL DNA IS INHERITED FROM THE MOTHER ONLY**



## Some diseases associated with mtDNA

- ▶ **MERRF** (Myoclonic Epilepsy with Ragged Red Fibres)
- ▶ **MELAS** (Myopathy, Epilepsy, Lactic acidosis, Stroke-like episodes)
- ▶ **LHON** (Leber's Hereditary Optic atrophy)
- ▶ **Kearn-Sayre** (eye problems, heart block, ataxia and loss of coordination)
- ▶ **Leigh syndrome** (rare severe brain disease in infancy, also heart problems)

# HOW THE EMBRYOS ARE MADE



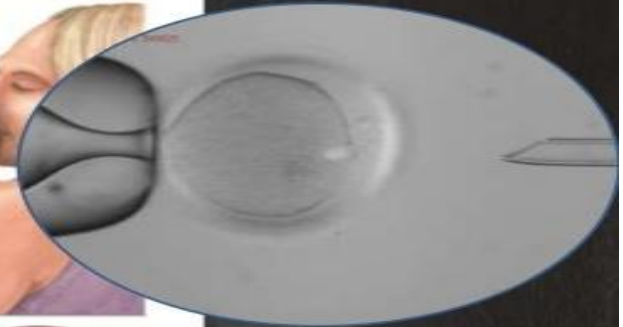
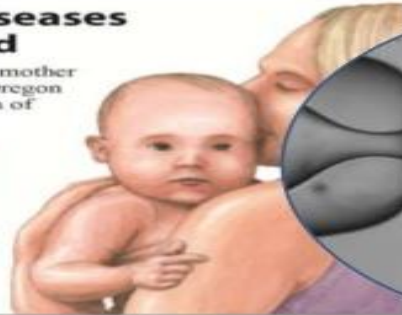
# New gene therapy for mitochondrial diseases a step closer thanks to ONPRC

## Gene therapy to prevent diseases passed from mother to child

More than 300 genetic diseases can be passed from mother to child because of mutated genes. Researchers at Oregon Health & Science University have developed a form of gene therapy to prevent these diseases.

### The mitochondria

Mitochondria are the powerstations of a cell, providing it with the energy to function. A mother's egg cell contains thousands of mitochondria, each containing its own DNA. If defective, the DNA in these cells can pass diseases from mother to child. Here's how researchers hope to use gene therapy to prevent these diseases:



### 1 Removing mother's nucleus

The cell nucleus holds chromosomes, which contain more than 99 percent of a person's DNA. The nucleus is removed from the mother's egg cell.

Mitochondria cells  
Mother's egg



Mother's nucleus removed

### 2 Removing nucleus from the donor's egg

The nucleus is also removed from an egg cell provided by a donor.

Donor's nucleus removed



Donor's egg

### 3 Inserting mother's nucleus in donor's egg

The nucleus removed from the mother's egg cell is inserted into the donor egg cell. Thus, the donor's normal mitochondria replaces the mother's defective mitochondria containing mutated DNA.

Donor's egg



Mother's nucleus inserted

### 4 Fertilizing the egg

A sperm cell is injected to fertilize the egg. The cell is then re-implanted into the mother and develops into a healthy baby.

Donor's egg



Egg fertilized

Source: Mitallipov Lab/OHSU

Eric Baker/OHSU

**Thanks for your listening**

**Dr. Ayad**