

BIO-373  
Genetics & Genomics

**Extranuclear  
inheritance**

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# Extranuclear inheritance

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- Transmission of genetic information to offspring through the cytoplasm and not the nucleus
  - Varieties in extranuclear inheritance
    - **Organelle heredity**
      - Mitochondria or chloroplasts
    - **Infectious heredity**
      - Symbiotic or parasitic association with microorganism
      - Inherited phenotype due to microbe in host's cytoplasm
    - **Maternal effect**
      - Influence of nuclear gene products present in oocyte
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# Outline

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1. Organelle heredity
  2. Human mtDNA and mitochondrial diseases
  3. Maternal effect and infectious heredity
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# **1. Organelle heredity**

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# Endosymbiotic theory

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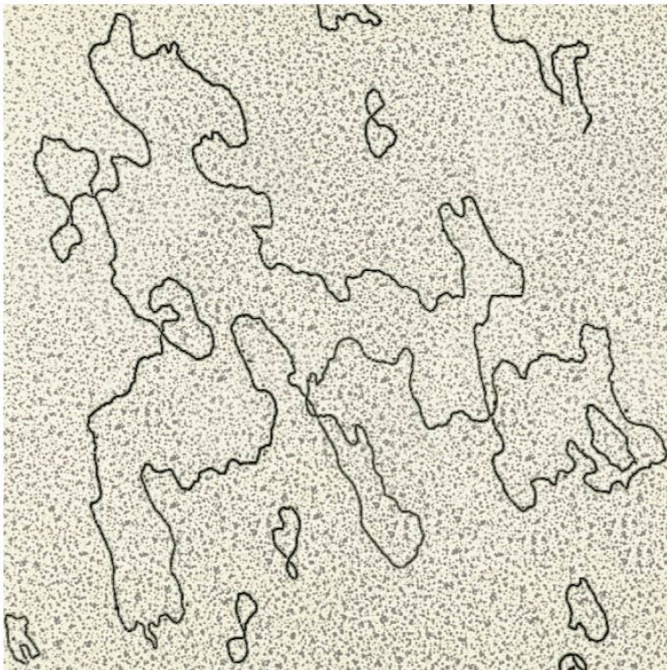
- **Mitochondria and chloroplasts** (organelles) arose independently 2 billion years ago from free-living bacteria
  
  - **Main points of endosymbiotic theory**
    - Bacteria were engulfed by larger eukaryotic cells
    - Beneficial symbiotic relationship developed
    - Bacteria lost ability to function autonomously
    - Eukaryotic cells gained oxidative respiration and photosynthesis
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# DNA in chloroplasts and mitochondria

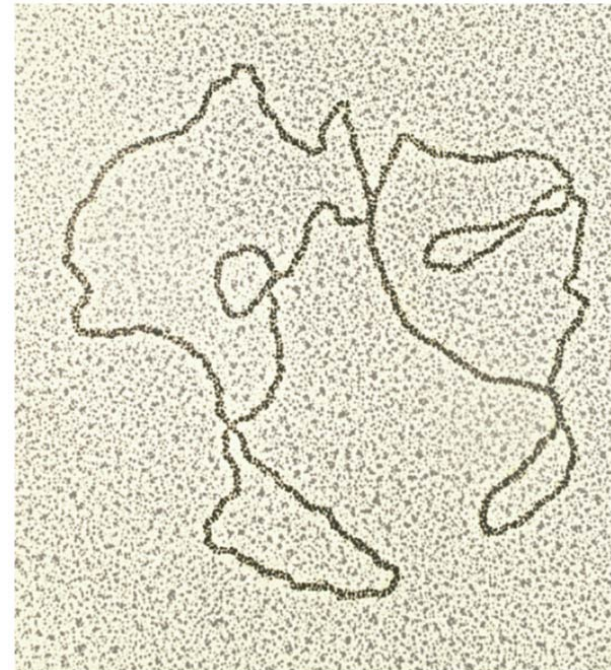
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- DNA in mitochondria and chloroplasts (double-stranded circular DNA) is unlike DNA seen in the nucleus of eukaryotic cells

**cpDNA**



**mtDNA**



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**TABLE 9.1** The Size of mtDNA in Different Organisms

Organism	Size (kb)
<i>Homo sapiens</i> (human)	16.6
<i>Mus musculus</i> (mouse)	16.2
<i>Xenopus laevis</i> (frog)	18.4
<i>Drosophila melanogaster</i> (fruit fly)	18.4
<i>Saccharomyces cerevisiae</i> (yeast)	75.0
<i>Pisum sativum</i> (pea)	110.0
<i>Arabidopsis thaliana</i> (mustard plant)	367.0

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# mtDNA mutations

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- **mtDNA is highly susceptible to mutations**
    - No structural protection from histones
    - mtDNA repair mechanism limited
    - High concentrations of reactive oxygen species (ROS) generated by cell respiration
      - ROS is toxic—damages organelle contents (proteins, lipids, mtDNA)
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# Chloroplast DNA variation

- ***Chlamydomonas* (unicellular alga)**
  - Excellent model system for studying organelle heredity
  - Has a single large chloroplast with 75 copies of circular double-stranded DNA
  - **Streptomycin resistance** has been shown to be encoded in cytosolic DNA (i.e. in chloroplast genome)
  - Studies by Ruth Sager (1954): differences in reciprocal crosses with susceptible strains  $\Leftrightarrow$  trait passed through female parent



$str^R mt^+ \times str^S mt^-$



$1/2 mt^+$	$1/2 mt^-$
all $str^R$	

$str^S mt^+ \times str^R mt^-$



$1/2 mt^+$	$1/2 mt^-$
all $str^S$	

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## **2. Human mtDNA and mitochondrial diseases**

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# mtDNA in humans

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## ■ Human mtDNA

- Double-stranded DNA, 16,569 base pairs
- 5-10 copies per mitochondrion
- Coding for 2 rRNA, 22 tRNA and 13 proteins required for aerobic cellular respiration

	Total	Mito	Nucléaire
Complexe I	43	7	36
Complexe II	4		4
Complexe III	11	1	10
Complexe IV	13	3	10
Complexe V	16	2	14
	87	13	74

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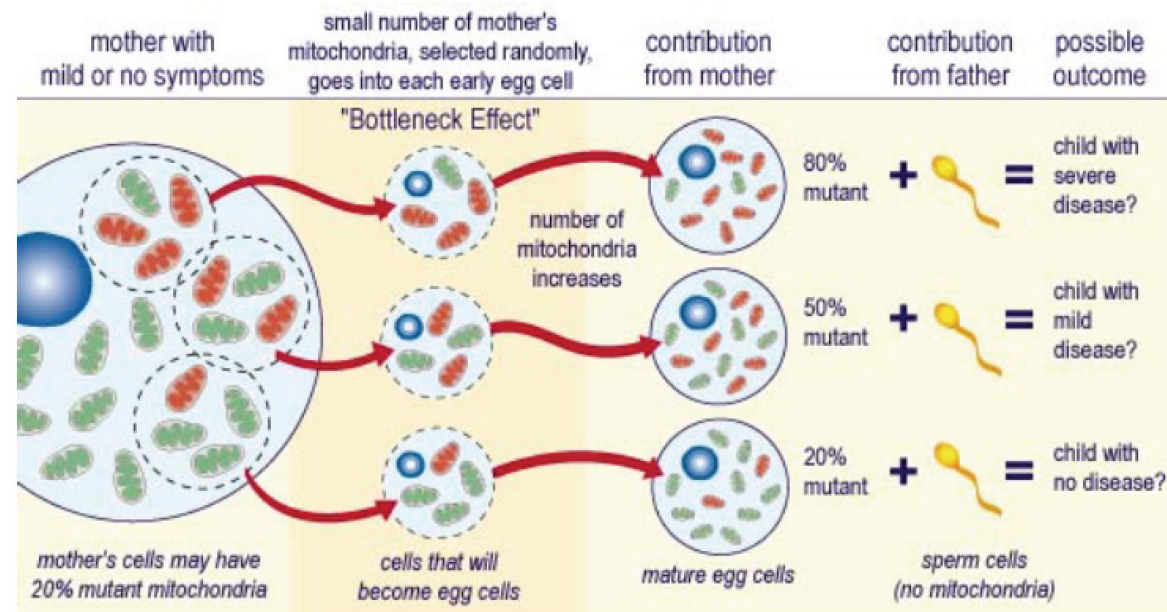
# mtDNA human disorders

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- **Criteria for human disorder to be attributed to mtDNA**
    - Maternal inheritance pattern
    - Disorder reflects a deficiency in the bioenergetic function of organelle
    - Mutation in one or more mitochondrial gene
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# mtDNA heteroplasmy

- If mutation is present in a subset of mitochondria present in the zygote, they will be found at various levels in adult cells
- This “mixture” of normal and abnormal organelles is called **heteroplasmy**
- Very variable clinical presentation, hard to do genetic counseling

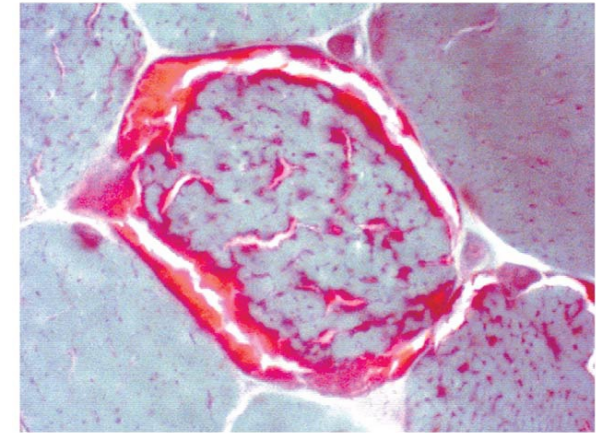


# Example of human disease: MERRF

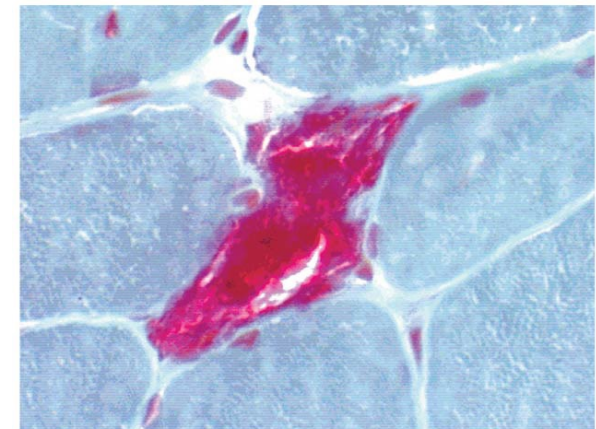
## ■ Myoclonic epilepsy and ragged-red fiber disease

- Pattern of inheritance consistent with maternal transmission
- Ataxia (lack of muscular coordination), deafness, dementia, epilepsy
- “Ragged-red” skeletal muscle fibers: red color results from proliferation of abnormal mitochondria
- Due to a mutation in the *MT-TK* mitochondrial gene, which encodes a transfer RNA for Lysine - tRNA<sup>LYS</sup>

(a)



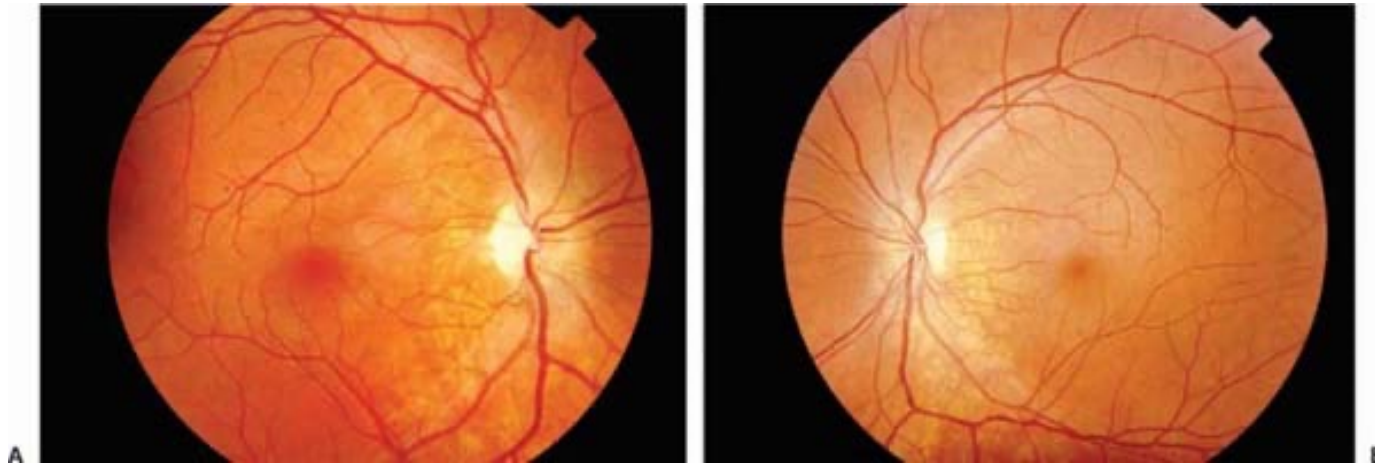
(b)



# Example of human disease: LHON

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- **Leber's hereditary optic neuropathy**
  - Pattern of inheritance consistent with maternal transmission
  - Bilateral blindness with rapid progression, age 20-30
  - Various mutations affecting oxidative phosphorylation
  - Most often sporadic (no familial history)



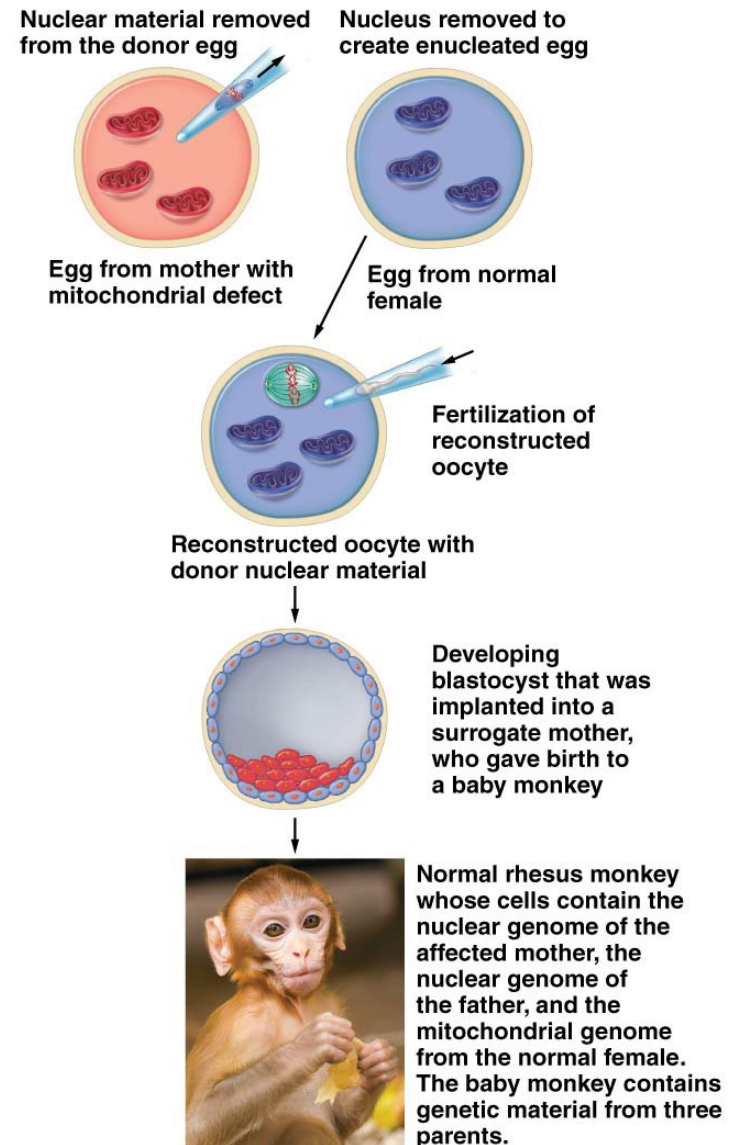
# Mitochondria, health and aging

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- **Mitochondrial dysfunction implicated in most human diseases**
    - Anemia
    - Type II diabetes
    - Infertility
    - Neurodegenerative diseases
    - Cancer
  - Likely due to the progressive accumulation of somatic mutations, leading to a loss of mitochondrial function
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# Prevention of mtDNA disorders?

- 1 in 5000 humans have mtDNA-based disease or are at risk for developing one
  - Can be detected by genetic testing
  - New therapies can prevent transmission of mtDNA mutations to offspring
  - Mitochondrial swapping in oocytes (“3 parents”)



# 'Landmark' study: three-person IVF leads to eight healthy children

Long-awaited results suggest that mitochondrial donation can prevent babies from inheriting diseases caused by mutant mitochondria.

By [Ewen Callaway](#)



<https://www.nature.com/articles/d41586-025-02276-5>

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### **3. Maternal effect and infectious heredity**

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# Maternal effect

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- Offspring's phenotype is under control of nuclear gene products present in egg
  - Nuclear genes of female gamete transcribed; genetic products accumulate in egg's cytoplasm
  - Products distributed among newly formed cells, influencing patterns/traits established early in development
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# Maternal genetic effects in freshwater snail

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- ***Lymnaea peregra***

- Phenotype: direction of shell coiling (right-handed vs left-handed)
- Genetics: single autosomal locus (D dominant and d recessive)
- Maternal effect: the mother's genotype determines the offspring's coiling because the oocyte cytoplasm contains maternal products that preset the direction of spiral cleavage.
- Maternal effect:
  - Mother DD or Dd → all offspring right-handed; regardless of their own genotype
  - Mother dd → all offspring left-handed; regardless of their own genotype
- Shell coiling is set by the mother's D/d genotype (maternal effect), and an individual's own D/d genotype doesn't affect its shell; only the shells of its offspring.



# Infectious heredity

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- **Definition:** A heritable phenotype caused by an infectious agent in the cytoplasm (eg, virus, bacterium), not by a nuclear or mitochondrial allele
  - **Key features:**
    - Vertical transmission through gametes (often strongly maternal, sometimes via both eggs and sperm)
    - Non-Mendelian segregation in crosses
    - May be mutualistic, commensal, or parasitic; expression can depend on host genotype and agent strain
  - **Example:**
    - *Drosophila* flies infected with the sigma virus (SIGV) become hypersensitive to CO<sub>2</sub>; after CO<sub>2</sub> anesthesia infected flies die, uninfected recover
    - SIGV is transmitted through gametes (eggs and sperm); cytoplasmic non-Mendelian inheritance
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