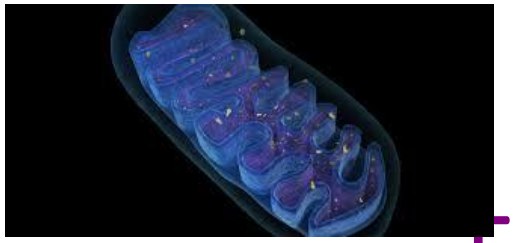


# Extranuclear Inheritance
# Lecture 18

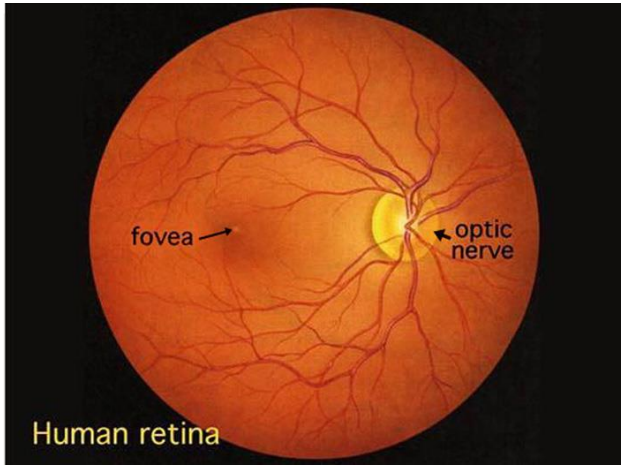
SLE254 Genetics and Genomics

Chapter 9 Concepts of Genetics 12th ed

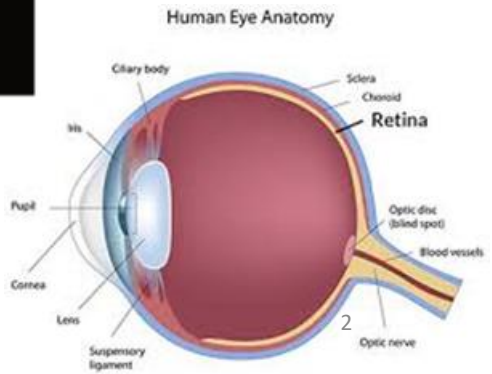
pp 234-250


# Case history of Frank Fletcher

- Frank Fletcher, 22 years old, electrician
- Noticed his vision was blurred and colours seemed paler than usual
- Perfect vision until that time
- Optician noticed that Frank's retina was showing signs of change




- Disk swelling in the retina (papilloedema)
- Retinal blood vessels abnormal



# Case history of Frank Fletcher

- His central vision became progressively worse over the next few months and he had to give up work

- **His mother's vision was fine** but her brother (**his uncle**) had been blind since he was 28

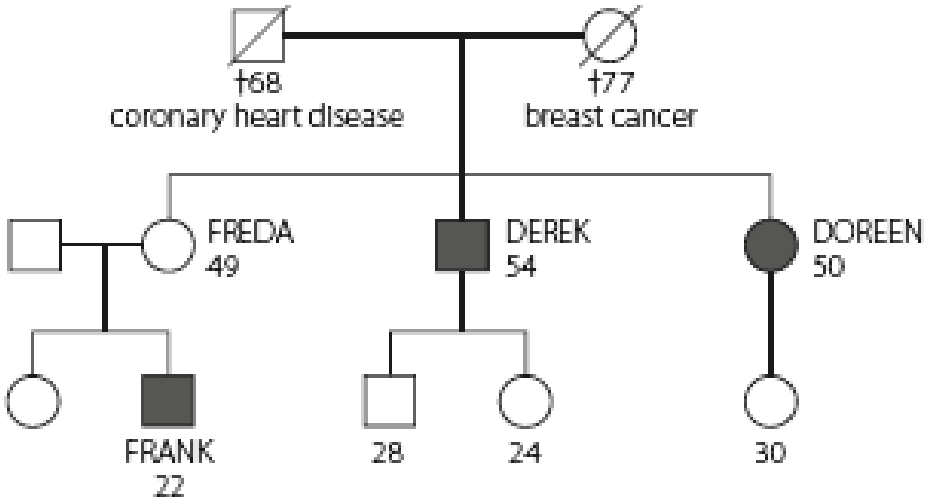
- His mother's sister (**his aunt**), Doreen, has serious visual defects since age 45 but with a slower progression than Frank
  - Doreen was also found to have some heart rhythm problems

# Frank's diagnosis

- Because of the family history, Frank attended a genetics clinic
- Diagnosed with **Leber Hereditary Optic Neuropathy (LHON)**
- Key points that lead to the diagnosis:
  - The nature of the eye problem
  - The **rapid progression in affected males**
  - Later onset and **milder symptoms in females**
  - Heart rhythm problems in Doreen
- Frank was shocked by the diagnosis, but was particularly concerned about whether he would pass on the condition

# Frank's pedigree

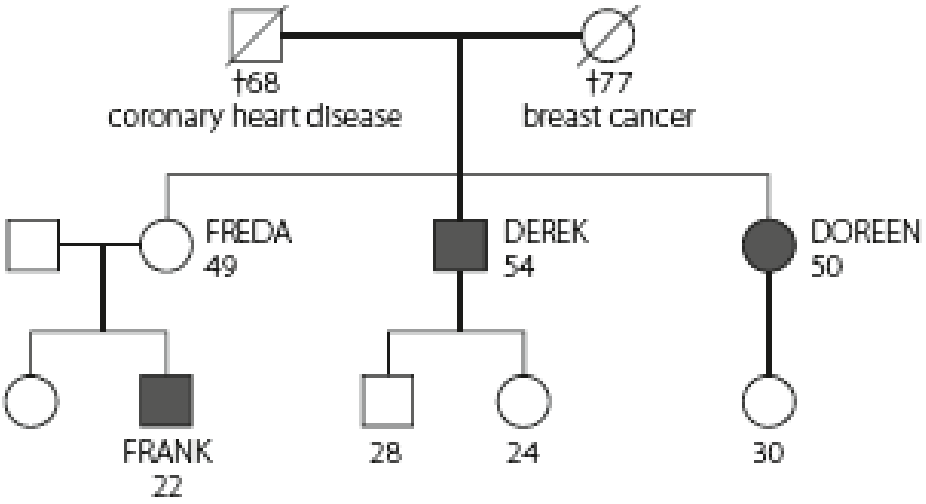
- Pedigree difficult to interpret
  - Considered X-linked recessive inheritance, but Doreen affected so less likely
  - Still possible though – Doreen could be a manifesting female carrier with milder problems than males
  - Also considered X-linked dominant inheritance and **mitochondrial inheritance**



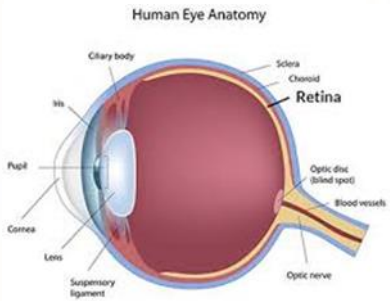

? Milder than males

# Frank's pedigree

- **Mitochondrial inheritance:**
  - Vertical transmission pattern
  - Children of **affected men are never affected**
  - All **children of affected women will be affected**, but the degree of severity is extremely variable



# Leber hereditary optic neuropathy




**Frank's retina** – 3 weeks after reduction in vision noticed

- Hyperemia of disc with blurred margins

**Uncle's retina** – vision lost years ago

- Optic atrophy

**Normal retina**

# Leber hereditary optic neuropathy

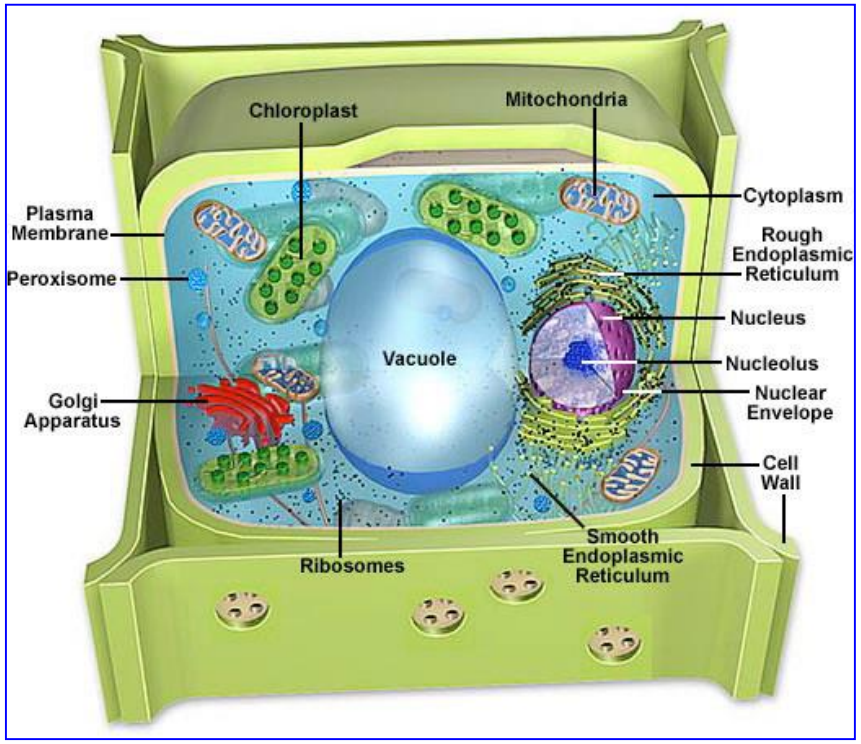
- First described in 1871 by the German ophthalmologist Theodore Leber
- 1 in 30,000 - 50,000, predominantly males affected
  - 2% of people on the blind register in Australia
- Bilateral subacute loss of central vision
  - Focal degeneration of the retinal ganglion cell layer and optic nerve
- **Mitochondrial genetic disease**

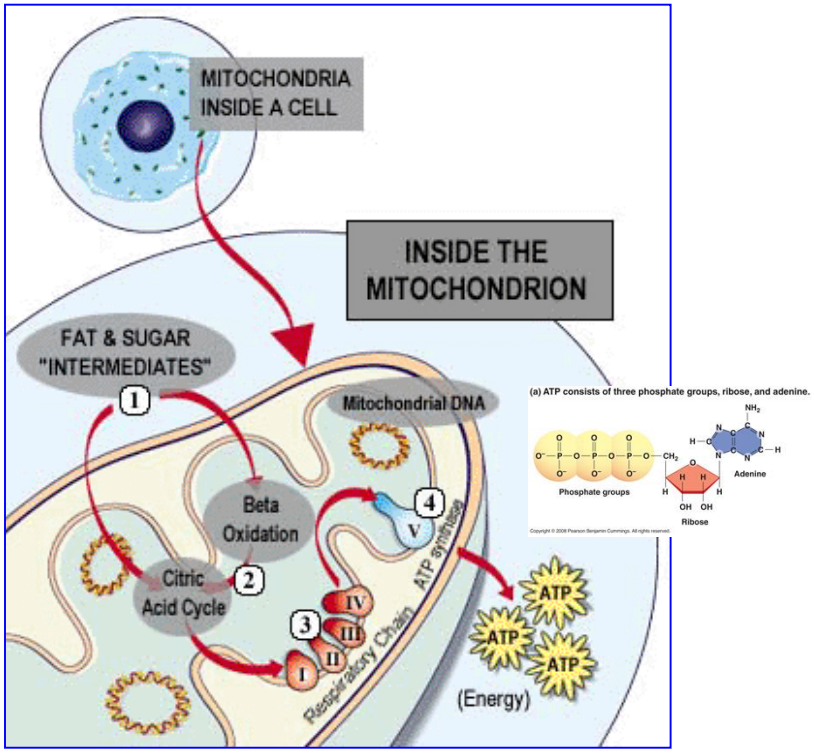
# LHON – the Frenchman Disease

- LHON affects large number of French-Canadians in Quebec
  - Example of a founder effect
- 1663, there was an unfavourable ratio of six male colonists to every European-born female
- King Louis XIV sent over 700 young single French women (“filles du roy,” or “King’s daughters”) between 1663 and 1673
- Many of the 5 million French-Canadians living in Quebec province are descendants of these women
- One woman carried a single nucleotide change in her mtDNA
  - Marrying one of the colonists in Quebec City in 1669, she produced five daughters who also all married in or near Quebec City
  - Today, as many as 90% of French-Canadians affected with LHON can trace their ancestry back to this woman

# Mitochondria

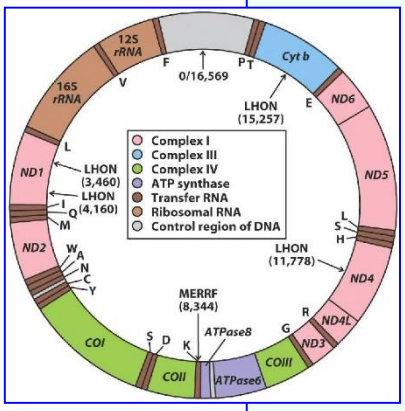
**Mitochondria are bacterial (alpha-proteobacteria) in origin**, common ancestor of eukaryotes contained a mitochondrion-like organelle

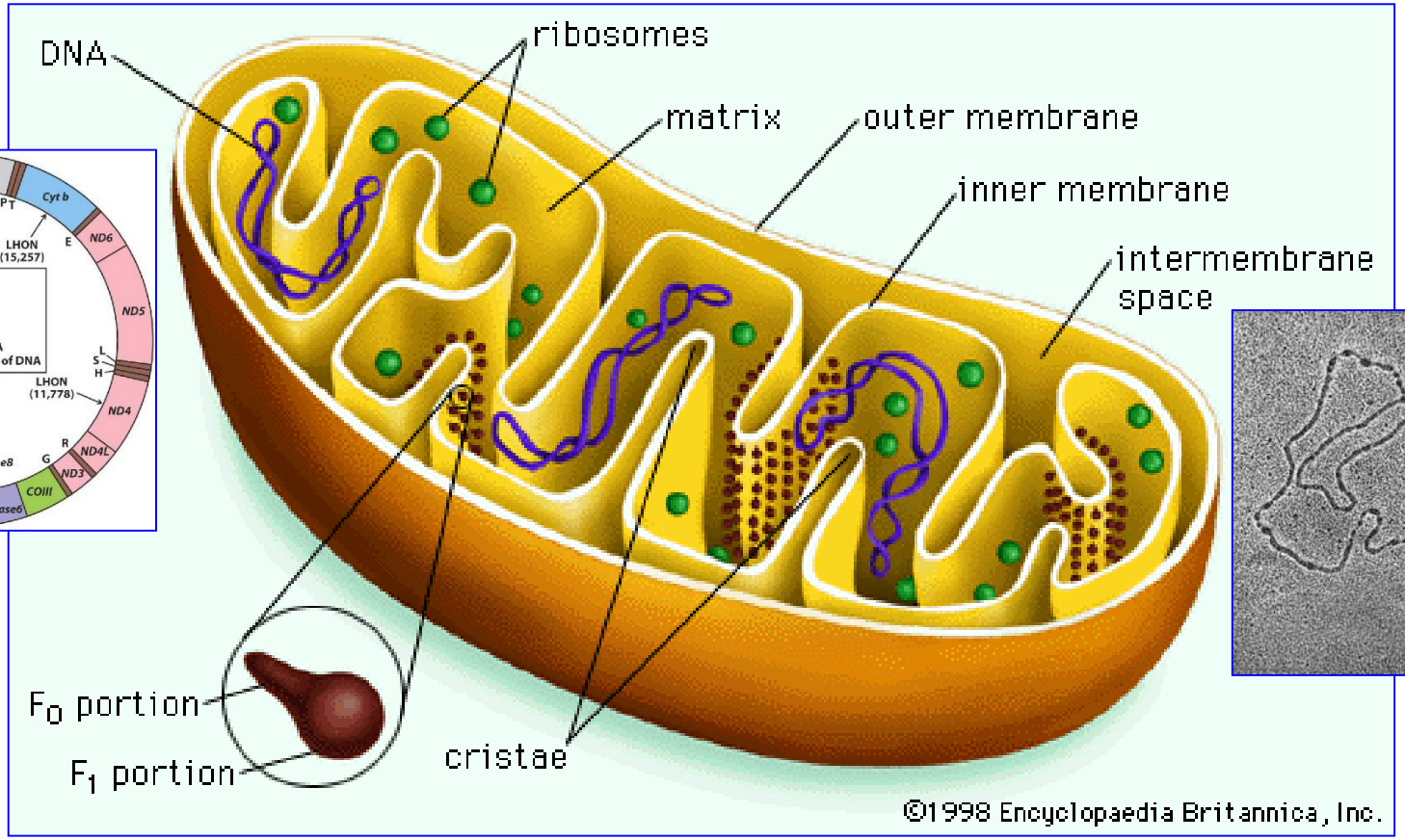



- Vertebrate oocyte: 100 million copies, Somatic cells: < 1000
- Can occupy app. 25% of the volume of the cytoplasm
- Site of oxidative phosphorylation and ATP synthesis
- Contain their own genome distinct from the DNA in the nucleus

# Mitochondrial DNA



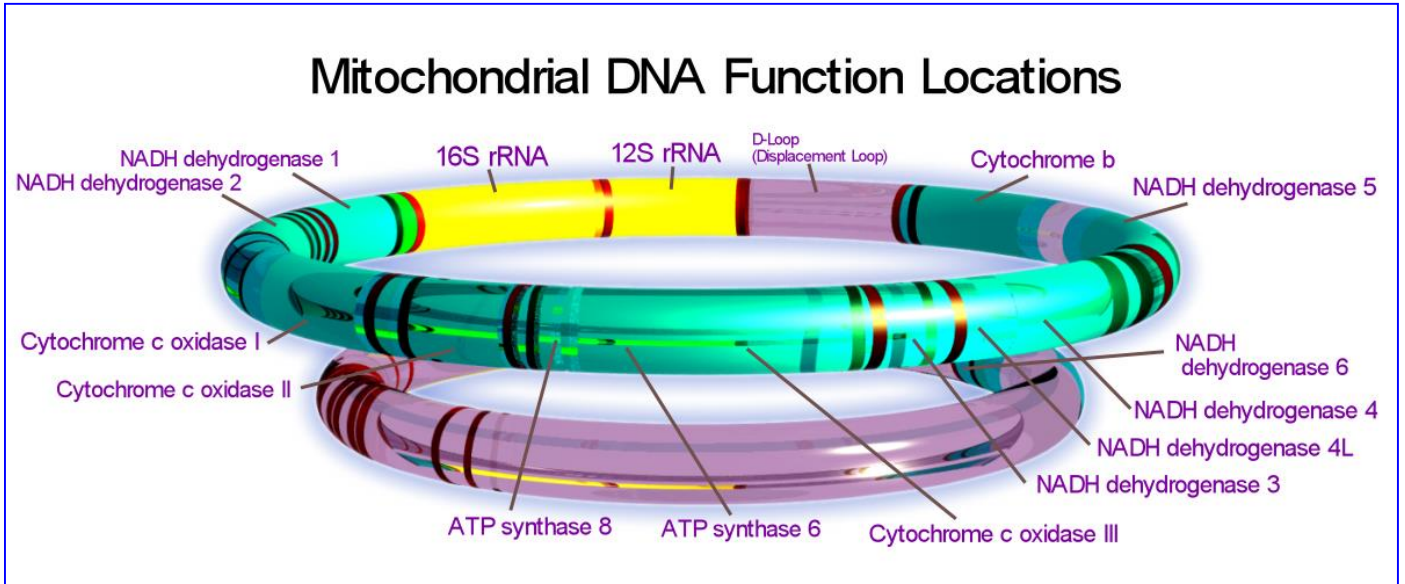






- Discovered in the 1960, DNA-like fibers within mitochondria
- **Most mtDNA molecules are circular** (exception: alga *Chlamydomonas reinhardtii* = linear)
- Cluster in nucleoids, attached to the inner membrane

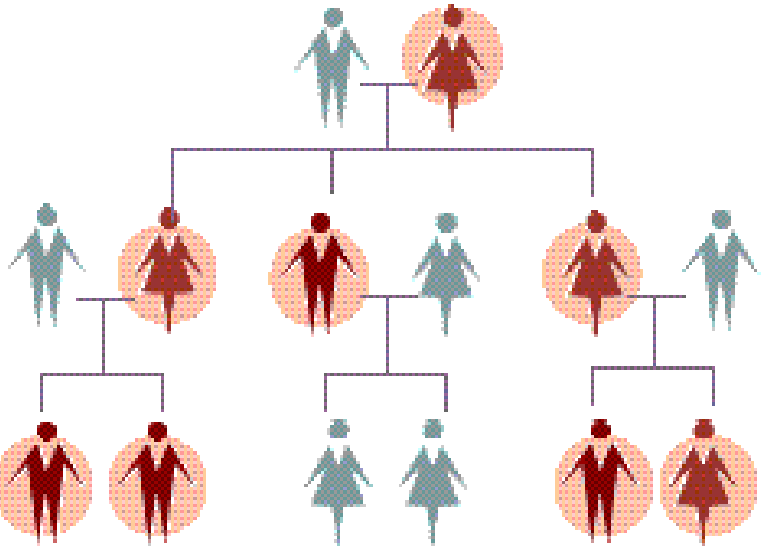
# Mitochondrial DNA

- Mitochondria have their own independent genome of about 16 Kb
- mtDNA is circular – bacterial origin
- 37 genes – tightly packed (no introns)
- **Most mitochondrial proteins are encoded by the nuclear genome**
  - Not all mitochondrial diseases are due to mutations in mitochondrial DNA
- ***LHON is one of the few diseases*** caused by mutations of mitochondrial DNA

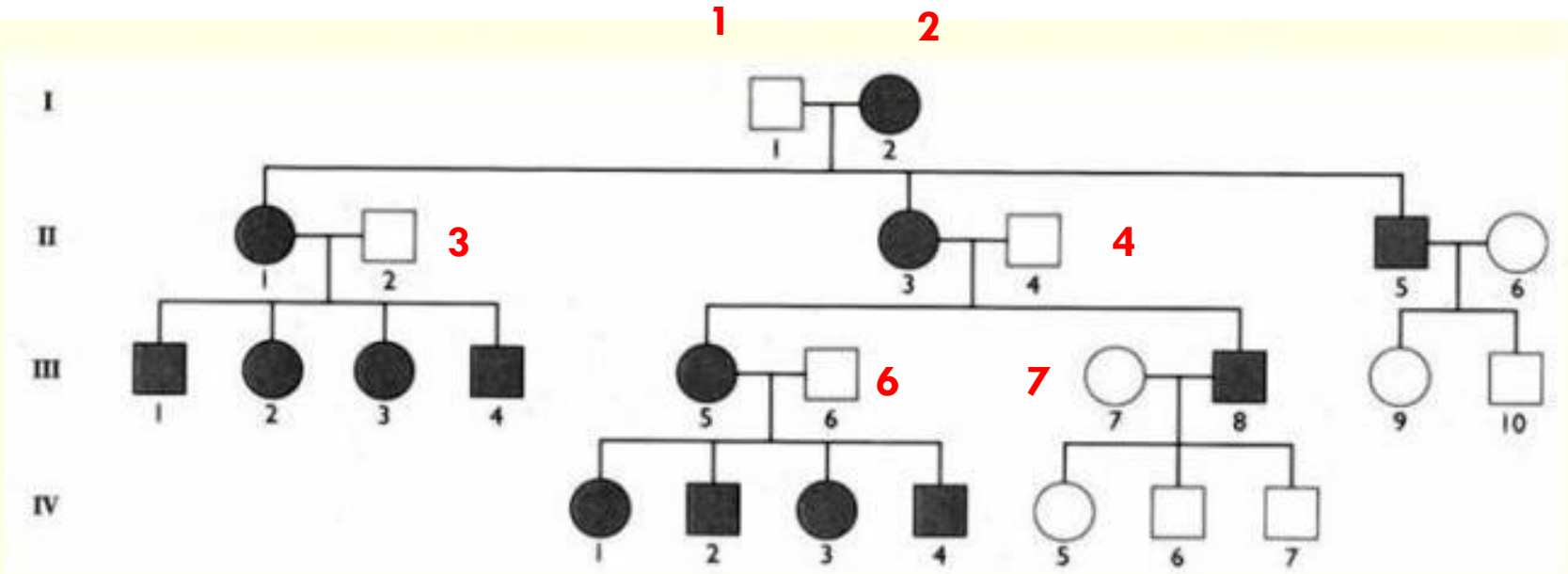


# Mitochondrial inheritance

- Mitochondria in an embryo derive from the **egg only**
  - The sperm does not pass on any mitochondria
- This gives rise to a maternal inheritance pattern
  - Both males and females can be affected, but only affected females pass on the trait
  - All siblings in a family will have the same mitochondrial DNA



# How many different types of mtDNA?




- Inheritance only through maternal lines
- Affected males do not pass on the genes

# Other mitochondrial diseases

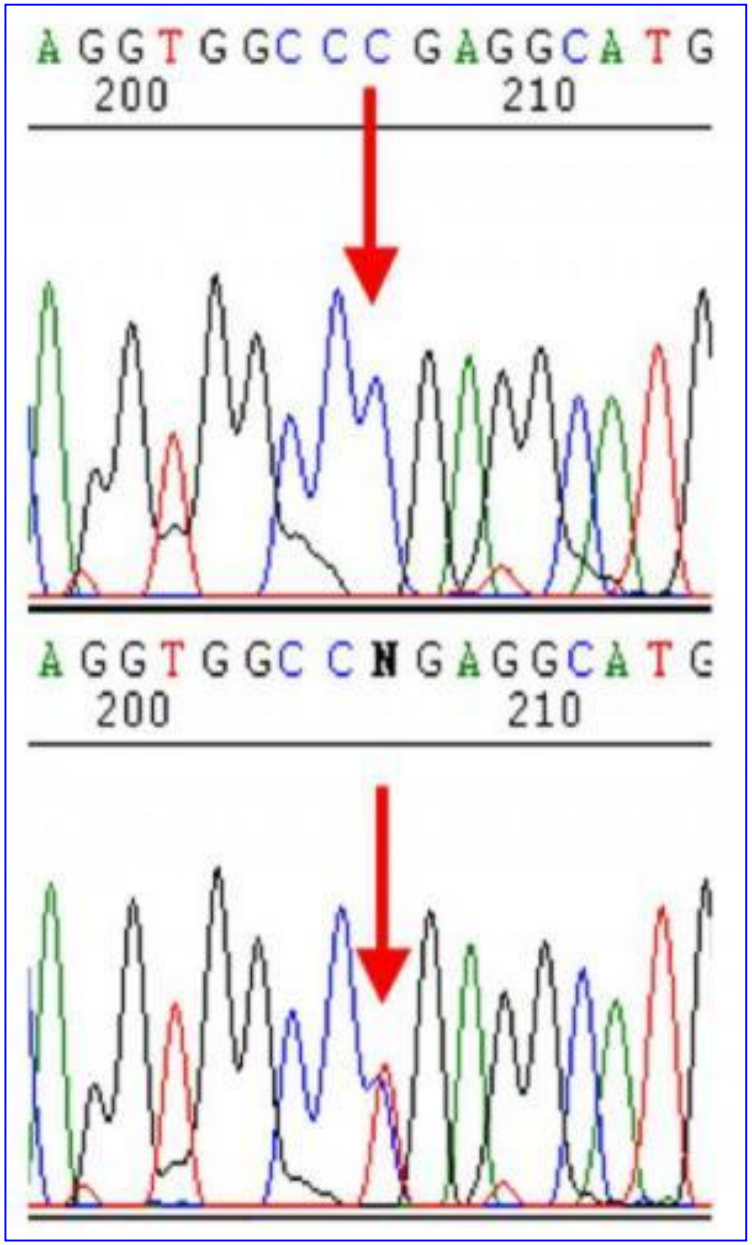
Online Mendelian Inheritance in Man

| Trait | Phenotype | OMIM Number |
|---|---|---|
| Kearns-Sayre syndrome | Short stature; retinal degeneration | 530000 |
| Leber optic atrophy (LHON) | Loss of vision in center of visual field; adult onset | 535000 |
| Leigh syndrome | Degradation of motor skills | 256000 |
| MELAS syndrome | Episodes of vomiting, seizures, and stroke-like episodes | 540000 |
| MERRF syndrome | Deficiencies in the enzyme complexes associated with energy transfer | 545000 |
| Progressive external ophthalmoplegia (PEO) | Paralysis of the eye muscles | 157640 |

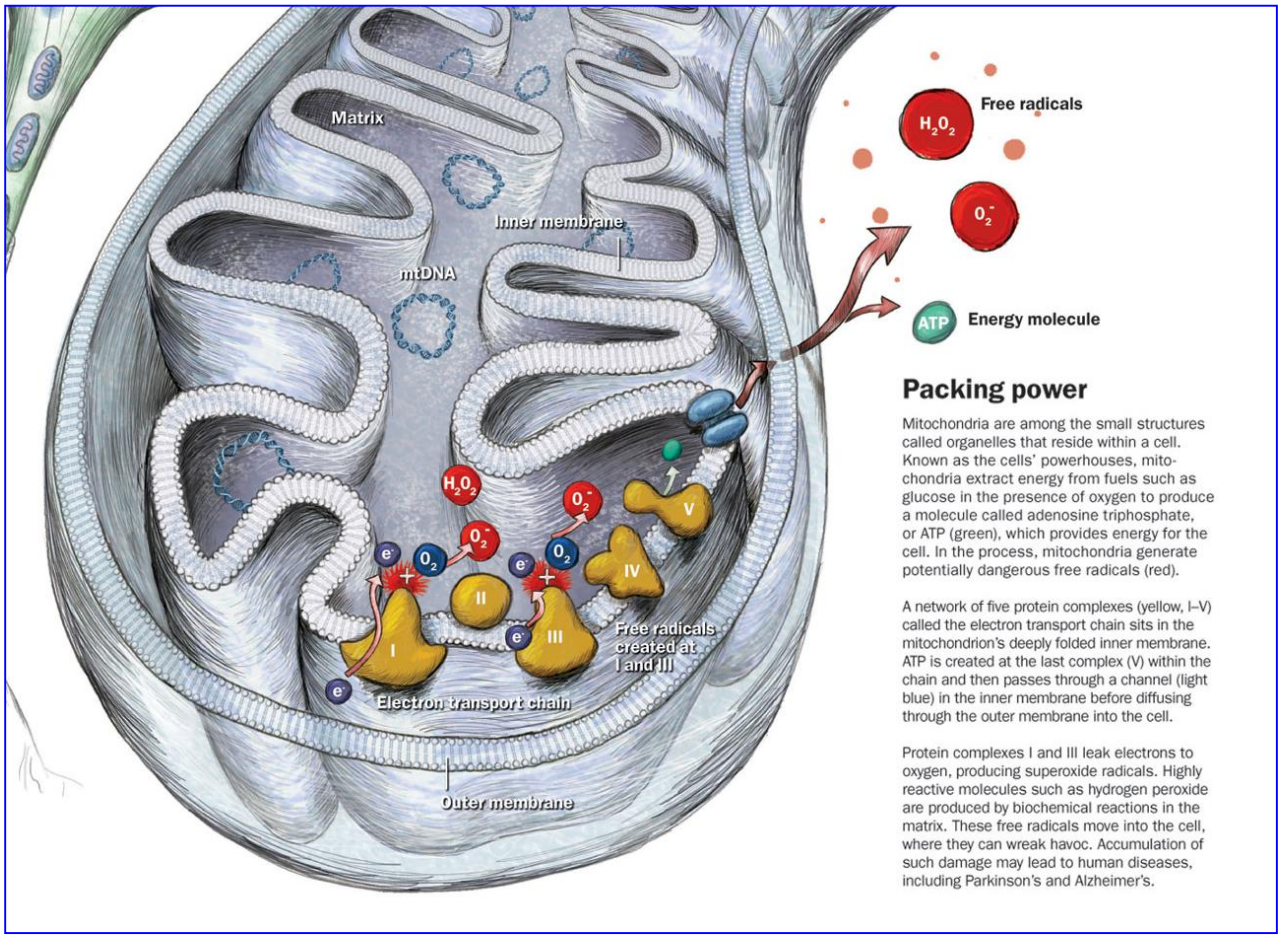
# Mutation in mitochondria

- Mitochondrial DNA exhibits a higher mutation rate than nuclear DNA in animals

- In animals the average substitution rate at silent sites in **mtDNA is 10 - 20 times higher than in the nuclear genome**



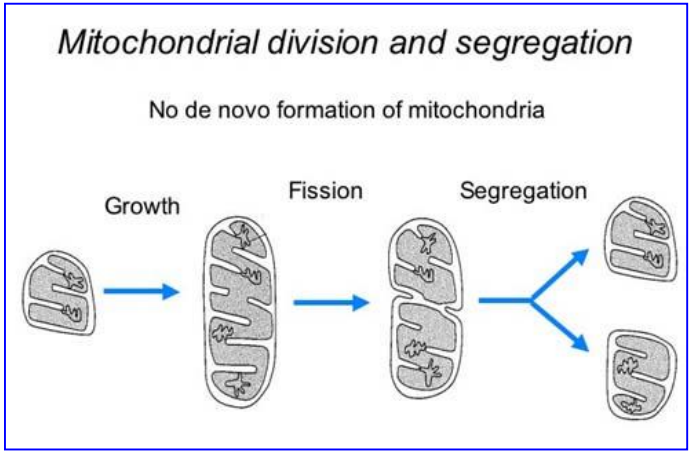
# Mutation in mitochondria



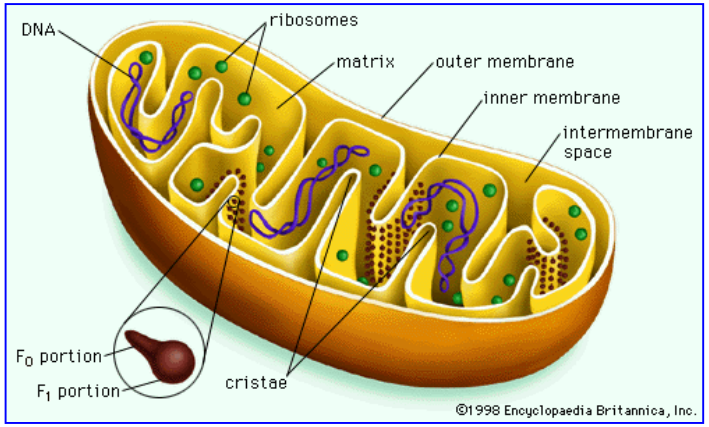

The increased mutation rate of mtDNA is caused by the lack of protective histones and proximity to the site of free radical-generating oxidative phosphorylation

# Mutation in mitochondria

- MtDNA **frequently replicates within non-dividing cells** increasing opportunities for replication errors per cell cycle




- Mitochondria contain multiple genomic copies increasing mutational targets



# Mitochondrial inheritance

## Assumption:

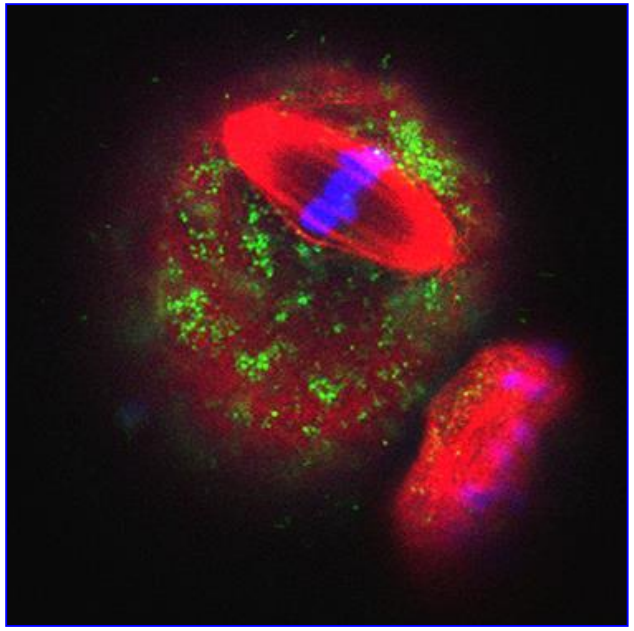
- Mitochondria in an embryo derive from the egg only
  - The sperm does not pass on any mitochondria (but see rare exceptions!)

- This gives rise to a **maternal inheritance pattern**
  - Both males and females can be affected, but only affected females pass on the trait
  - All siblings in a family will have the same mitochondrial DNA

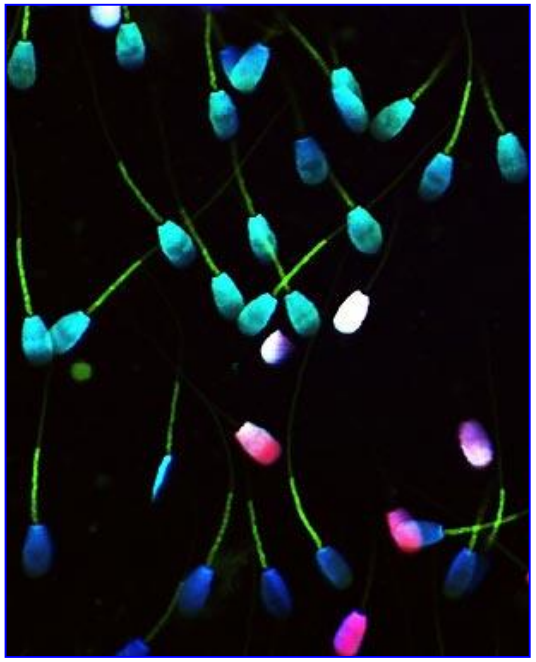
## BUT

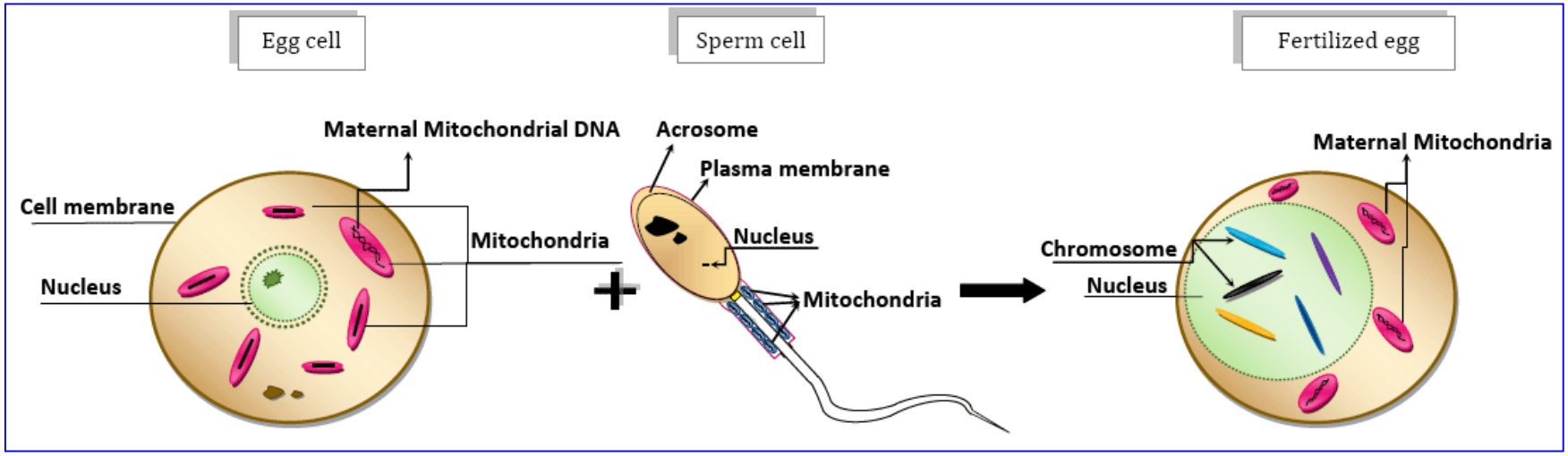
Some evidence exist for paternal inheritance!

# Death to male mitochondria



A sperm carries mitochondria in its tail as an energy source for its long journey to the egg

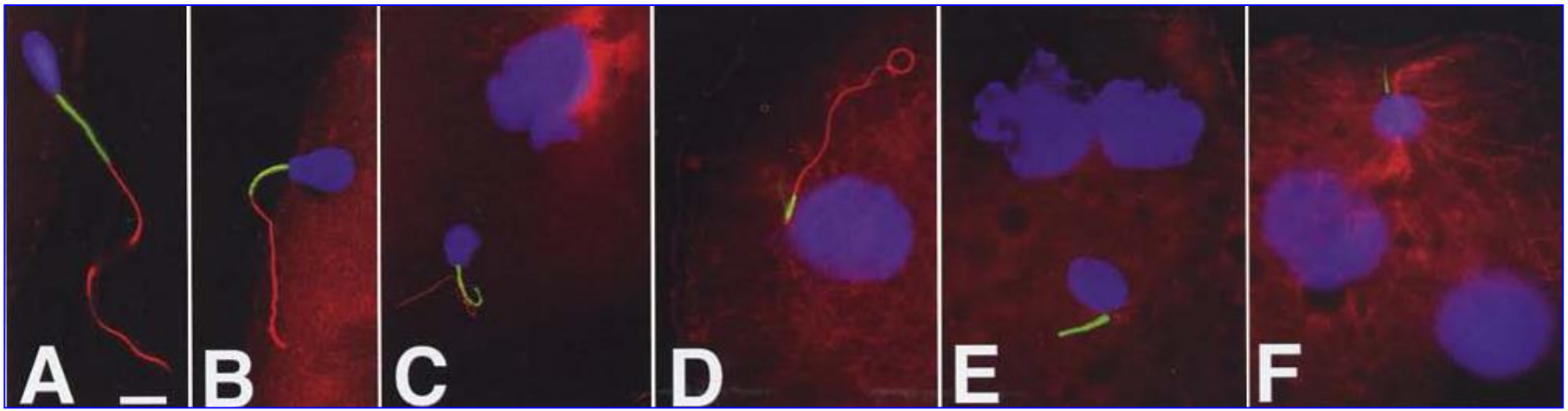




# Death to male mitochondria

Mammals: **Sheer numbers!**

100 paternal mitochondria enter the egg (containing 100,000 maternal mt) but are actively targeted and destroyed by a mechanism that recognizes the ubiquitin that sperm are tagged with



# mtDNA inheritance

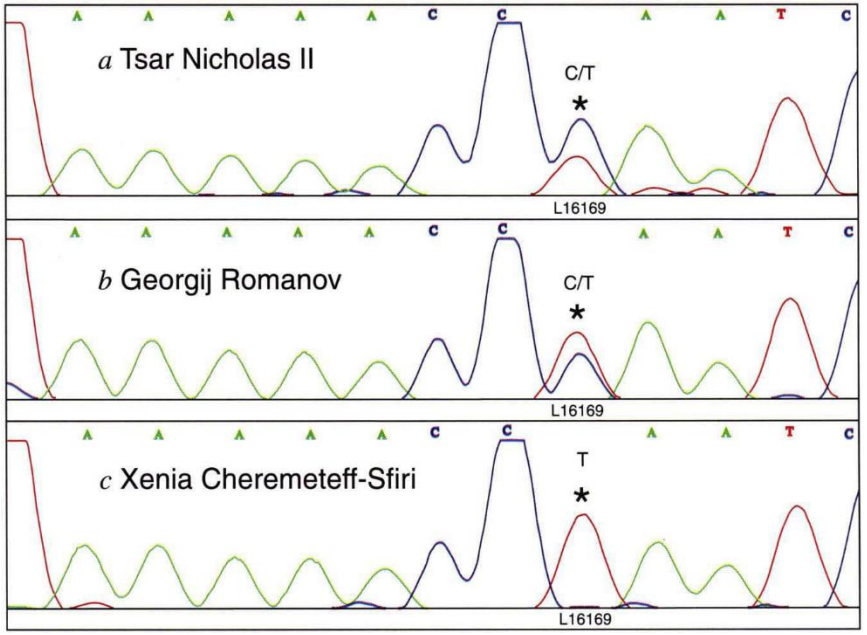
- Situations exist in which the mechanism for recognition of paternal mitochondria in the fertilized egg can fail, thus enabling **PATERNAL LEAKAGE** to occur

- Paternal leakage has been observed in a taxonomically wide variety of invertebrate and vertebrate species

# mtDNA inheritance important concepts:

## Heteroplasmy:

is the presence of a mixture of more than one type of an organellar genome (mitochondrial DNA) within a cell or tissue




## Homoplasmy:

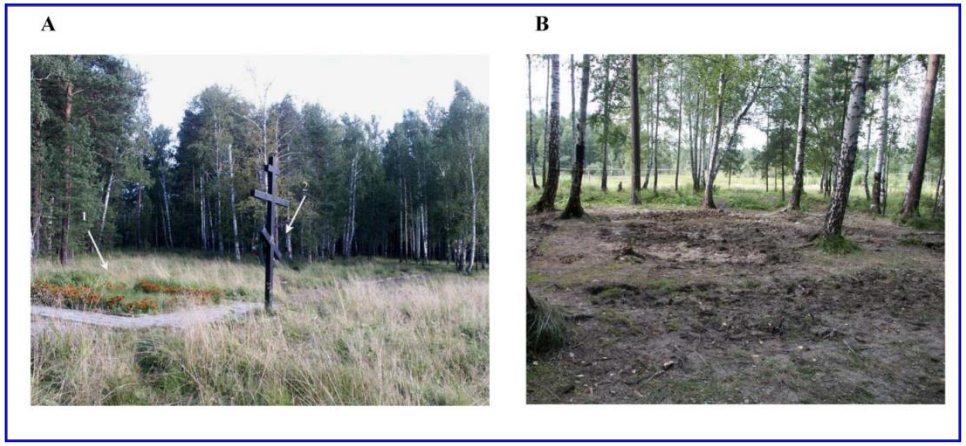
a state in which all the mitochondria of a cell or a tissue have the same genome, which may be either the wild type genome or a mutated one

# Mitochondrial heteroplasmy: a case study

Russia's last Tsar Nicholas II

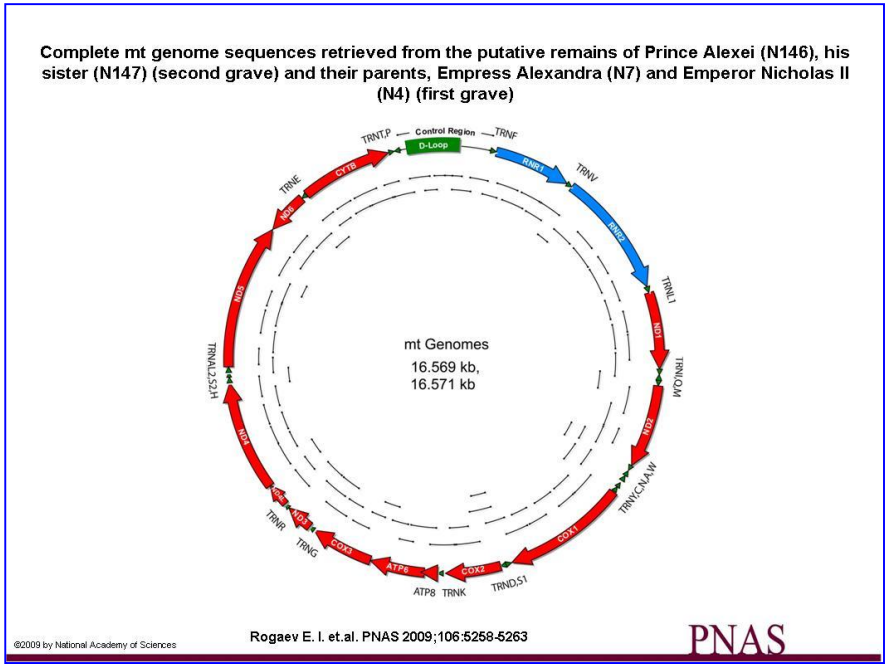
The entire family was executed by the Bolsheviks in July 1918, bodies had not been found, until July 1991

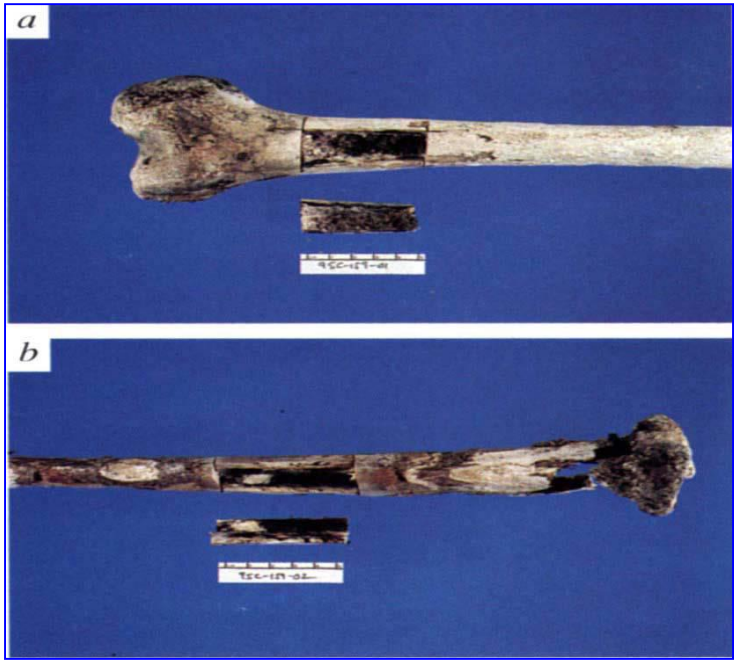
Ivanov et al. 1994&1996. Nat. Genet. 6: 130–136 & 12: 417–420.




Cobler et al. 2009. PlosOne 4 e4838-4847.

# Mitochondrial heteroplasmy: a case study

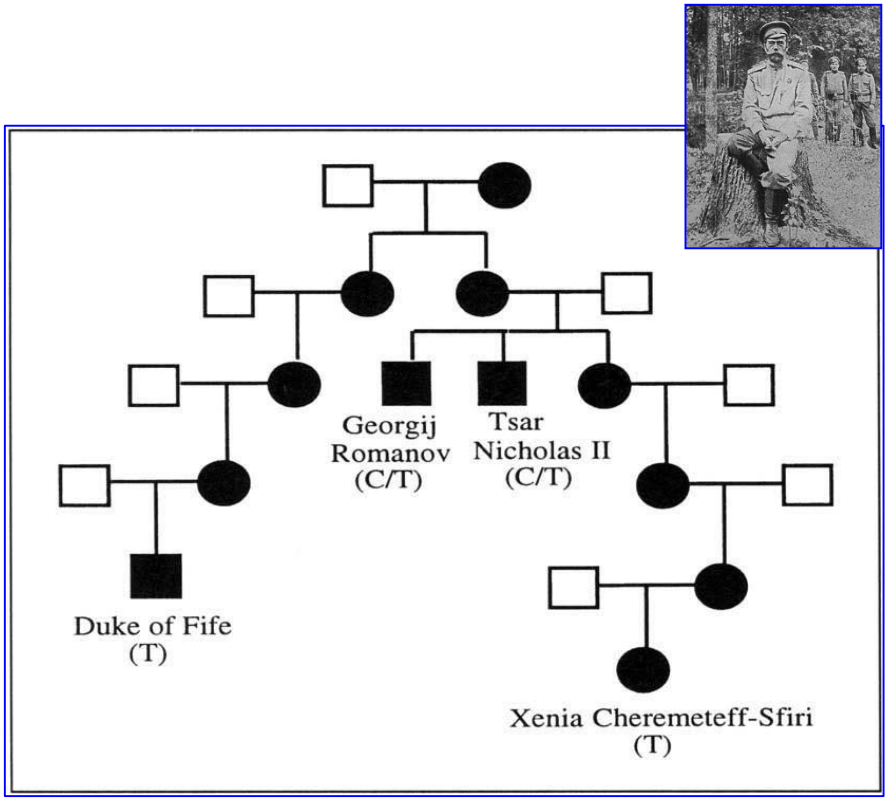


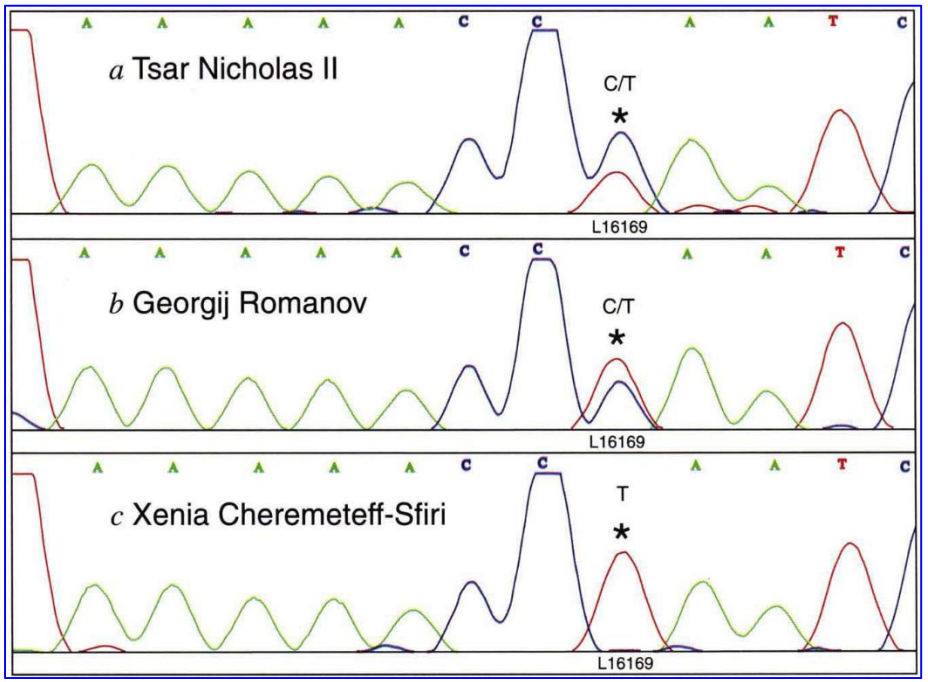




To identify the remains, mitochondrial DNA (mtDNA) samples were taken.

mtDNA from four female skeletons exactly matched those of **Prince Philip, a living maternal relative of Tsarina Alexandra**, providing strong evidence that the remains were those of the Tsarina and three of her daughters

# Mitochondrial heteroplasmy: a case study




The sample from the presumed skeleton of the Tsar was heteroplasmic, the mtDNA matched a maternal relative, except for one site where the 2 nucleotides were segregating.
Sequencing the mtDNA from the Tsar's brother Georgij Romanov showed heteroplasmy at the same position

# Maternal effect

The maternal genotype has a strong influence during early development

- The embryo is formed when a female gamete unites with a male gamete

- **Female gamete provides the cytoplasm for the developing embryo**

- Factors in the cytoplasm (released by the nuclear genes of the female) can have specific effects on the developing embryo =

**maternal effect**

# Maternal inheritance *vs* Maternal effect

## AN IMPORTANT DISTICNTION: Remember!

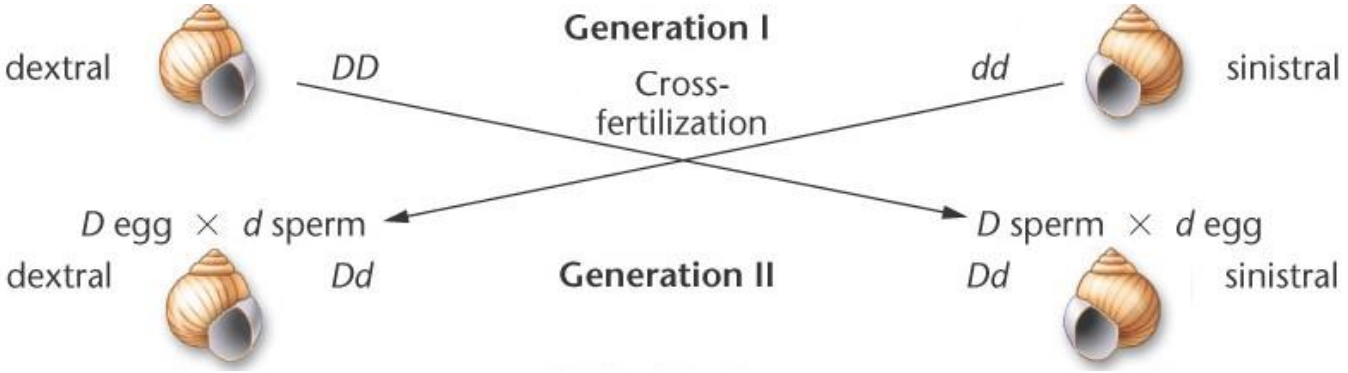
- The female cytoplasm also contributes the mitochondria for all animal species as well as the chloroplast for plant species.

- These two organelles contain DNA and control certain traits in the offspring.

1. Phenotypes controlled by **organelle genes** exhibit **maternal inheritance**

2. Phenotypes that are controlled by **nuclear factors found in the cytoplasm of the female** are said to express a **maternal effect- not dependent on genotype**

# The classic phenotype which exhibits maternal effects is coiling direction of snail shells. The coiling phenotype that is seen in the offspring is controlled by the genotype of the mother.

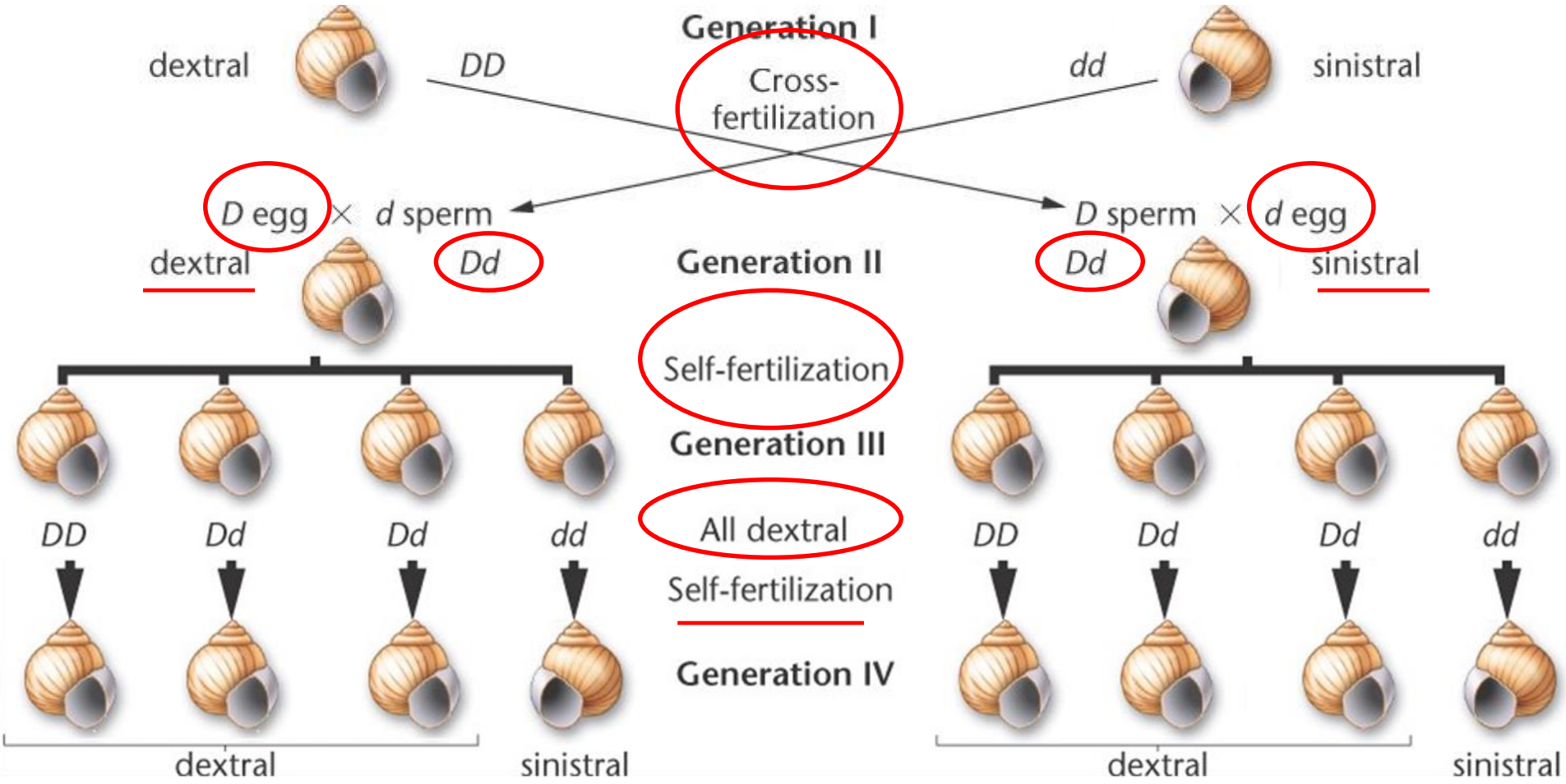



*D (dextral allele)*: causes right handed coil

***DD & Dd* females synthesize and store the D gene product in the oocytes**

d (*sinistral allele*): classic recessive mutant, **codes inactive gene product**

# **Maternal effect** - *Limnaea*




**The coiling pattern of the progeny snails is determined by the genotype of the egg donor parent, regardless of the phenotype of that parent.**



http://www.abcalphabet.in/wp-content/uploads/2017/01/09_13-maternal_effect-Limnaea_coiling1.jpg

# **Maternal effect** – *Limnaea*

Spindle orientation determined in the first cleavage division after fertilization determines the direction of the coiling

Maternal genes act on the developing eggs in the ovary – affecting spindle orientation

Ooplasm from dextral eggs injected into uncleaved sinistral eggs result in cleavage in a dextral pattern

Ooplasm from sinistral eggs injected into uncleaved dextral eggs result in cleavage in a dextral pattern

# **Maternal effect** – *Limnaea*

*D (dextral allele)*: causes right handed coil

d (*sinistral allele*): classic recessive mutant, codes inactive gene product

*DD & Dd* females synthesize and store the D gene product in the oocytes

Even if the oocyte contains only the d allele following meiosis and is fertilized by a d-bearing sperm, the resulting dd snail will be dextrally coiled (right handed)

**The coiling pattern of the progeny snails is determined by the genotype of the parent producing the egg, regardless of the phenotype of that parent.**