Special Topics on Genetics

Section 8: Non-Mendelian inheritance

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Ευρωπαϊκή Ένωση
Ευρωπαϊκό Κοινωνικό Ταμείο
ΕΠΙΧΕΙΡΗΣΙΑΚΟ ΠΡΟΓΡΑΜΜΑ
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Extranuclear inheritance (1/10)

Inheritance pattern of the characteristics that are controlled by organelles' genes :

- Mitochondria
- Chloroplasts (only in plant cells)

Extranuclear inheritance (2/10)

Early 20th century:

- Transfer of characteristics that do not follow the Mendel’s laws
- Uniparental inheritance
- Different results in reverse crossings

Thus the question arose:

Is there genetic material outside the nucleus?

In 1960s using Specific stains, Autoradiography and Electron Microscopy
Genetic material in the mitochondria and the chloroplasts
was detected

Extranuclear inheritance (3/10)

Genes of mitochondria and chloroplasts

They are referred to as:

- *Extrachromosomal genes*
- *Cytoplasmic genes*
- *Non-Mendelian genes*
- *Organellar genes*
- *Extranuclear genes*

Extranuclear inheritance (4/10)

Figure 1: Schematic illustration of a mitochondrion in transverse-section

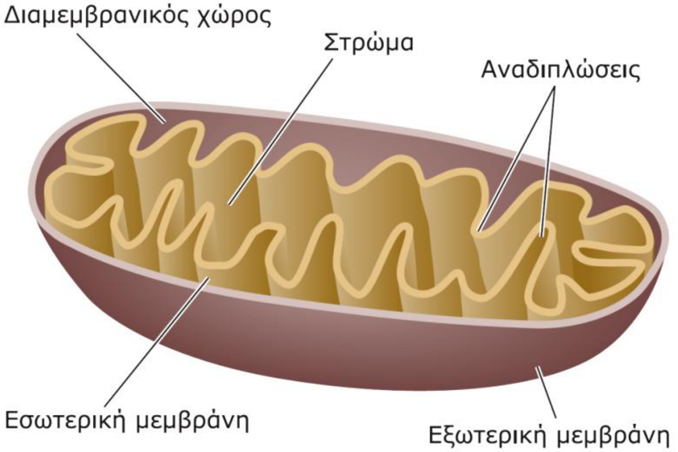
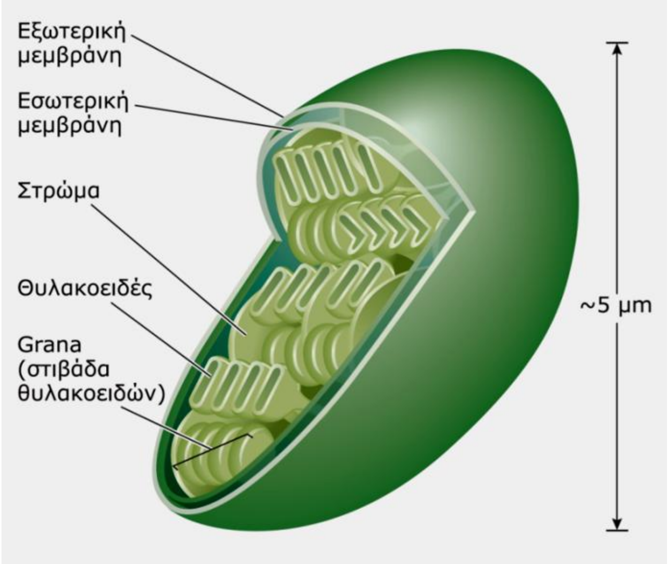


Figure 2: Schematic illustration of a chloroplast in transverse-section



Mitochondria: organelles which are found in the cytoplasm of all aerobic eukaryotic cells and are involved in cellular respiration

Chloroplasts: organelles which are found in the cytoplasm of green plants and photosynthetic primates and are involved in photosynthesis

Extranuclear inheritance (5/10)

Genetic material of mitochondria (mtDNA) and chloroplasts (cpDNA)

The genome of organelles has the following characteristics:

- Circular, double stranded, supercoiled DNA molecule
- Bare of histones
- The size of the mtDNA is stable to higher vertebrates, varies in lower animals and plants
- The size of cpDNA is stable

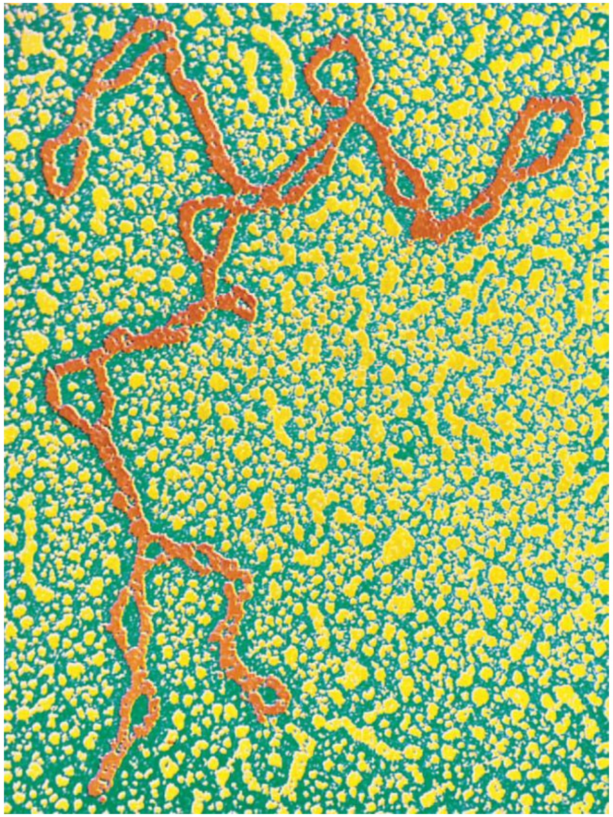


Figure 3: Electon micrograph of mitochondrial DNA

Extranuclear inheritance (6/10)

Genetic material of mitochondria and chloroplasts

	SPECIES	STRUCTURE	SIZE(kb)
mtDNA	Animals	Circular	12-20
	Higher plants	Circular	100-2000
	Algae	Circular	30-70
	Protozoa		
	Plasmodium	Circular	25
	Paramecium	Linear	40
cpDNA	Algae	Circular	120-200
	Higher plants	Circular	120-200

Extranuclear inheritance (7/10)

Genetic material of mitochondria

The mitochondrial genome usually consists of a single "chromosome“

In the majority of cases (such as human) mitochondrial genome is a circular, supercoiled molecule

But there are exceptions…

Thus in some species the mtDNA consists of:

- *Spizellomyces punctatus*: 3 types of circular molecules
- *Amoebidium parasiticum*: hundreds of types of linear molecules
- *Amoebidium parasiticum*: 1 linear molecule

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Extranuclear inheritance (8/10)

Genetic material of mitochondria

- The size of mitochondrial genome is usually between 15–60 kbp
Plasmodium sp: 6 kbp
Oryza sativa: 490 kbp

- The average of the mitochondrial genome genes are 40-50 genes

- The size of the mitochondrial genome is not always proportional to the genes content

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Extranuclear inheritance (9/10)

Genetic material of mitochondria and chloroplasts

- In each organelle there may be multiple copies of the genome, which are organized in nucleoids

- In each cell there may be tens to hundreds of organelles

Extranuclear inheritance (10/10)

Genetic material of mitochondria and chloroplasts

The Table below shows the amount of mt & cp DNA into various cells

SPECIES	CELLS	MOLECULES/ORGANELLE	ORGANELLES/CELL	% OF TOTAL DNA
mtDNA				
Rat	Liver	5-10	1000	1%
Human	Hela	10	880	3%
Yeast	-	40-150	1-45	15%
cpDNA				
Euglena		40	15	3%
Corn	Leaves	20-40	20-40	15%

Extranuclear inheritance-Mitochondrial DNA (1/15)

1981: Publication of primary structure of human and yeast DNA

- Human: 16569 bp
- Yeast: approximately 78000bp

Significant size difference - Similar genetic information

Extranuclear inheritance- Mitochondrial DNA (2/15)

Human

2 rRNA genes (12S, 16S)

22 tRNA genes

13 genes for proteins: COX I, II,III, Ctb, ATPase 6,8, NDU 1-7

control region or D-loop

Saccharomyces

2 rRNA genes (21S, 15S)

30 tRNA genes

8 genes for proteins: COX I, II,III, Ctb, ATPase 6,9, ribosomal protein and splicing enzyme

control region or D-loop

The most important difference: presence of introns and non-coding regions in the mitochondria of *Saccharomyces*!

Extranuclear inheritance-Mitochondrial DNA (3/15)

The mitochondrial DNA of higher vertebrates is an **economy model** as exhibits the following characteristics :

- ➢ It does not include introns
- ➢ It does not include spacer DNA
- ➢ It includes only 22 tRNA

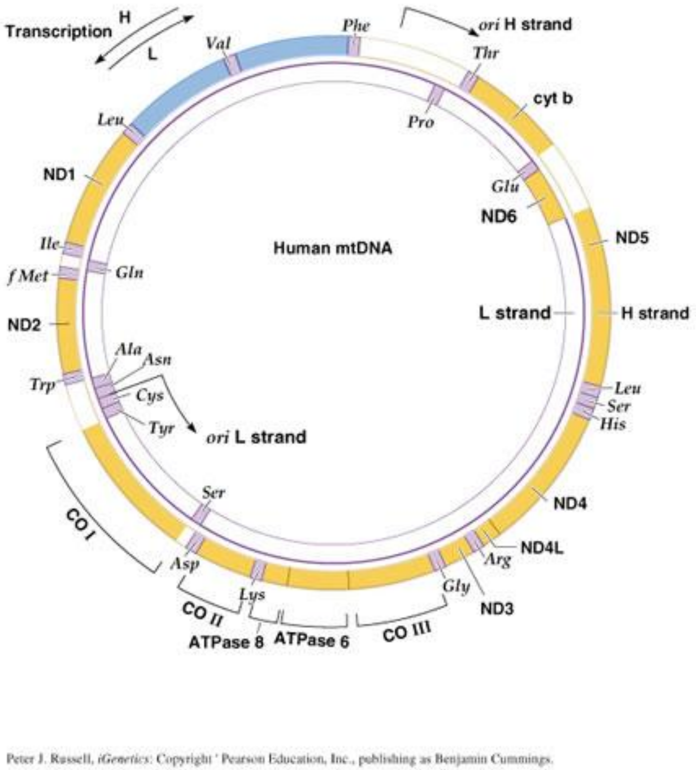


Figure 4: Map of the genes of the human mtDNA

Extranuclear inheritance-Mitochondrial DNA (4/15)

There are more than 600 mitochondrial or associated with mitochondria proteins!

Proteins encoded by genes of the nucleus :

- DNA polymerase
- RNA polymerase
- Proteins which regulate replication - transcription
- Ribosomal proteins
- Protein translation factors
- Peptide subunits COX, NADH, ATPases etc

Extranuclear inheritance-Mitochondrial DNA (5/15)

Replication

✓ Semi-conservative replication

✓ Specific mitochondrial polymerase (γ)

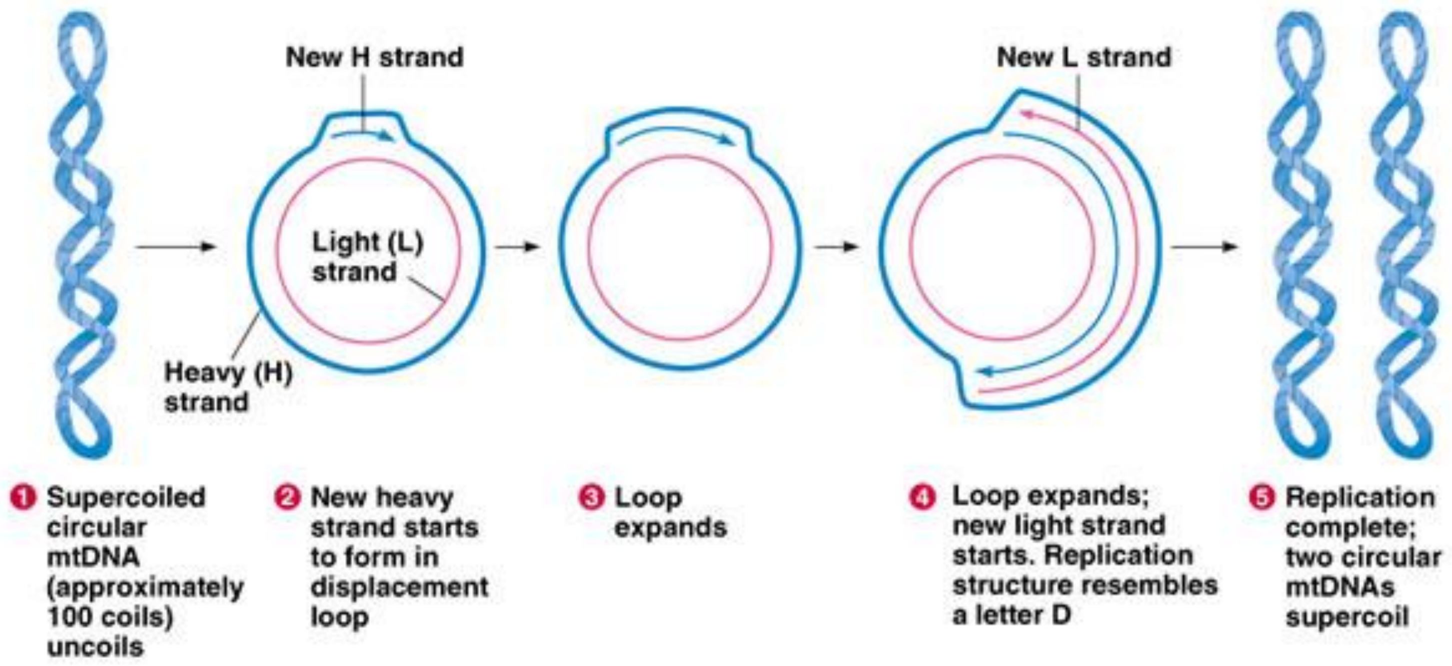
✓ The replication is independent of the nuclear DNA, throughout the cell life cycle, but depends on the nuclear DNA

✓ Model of D-loop displacement

Extranuclear inheritance-Mitochondrial DNA (6/15)

Replication

Figure 5: Model replication of mitochondrial DNA, showing the formation of the D loop.



Extranuclear inheritance-Mitochondrial DNA (7/15)

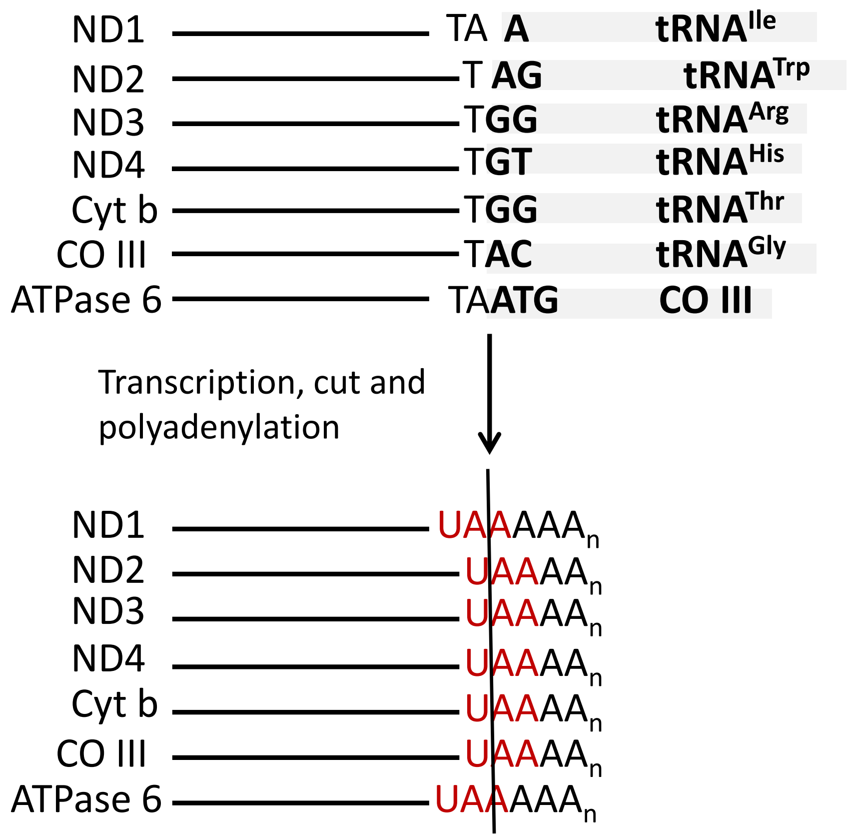
Transcription

Vertebrates

- Two promoters
- 2 large RNA molecules
- Genes for tRNAs are inserted between the genes encoding the rRNAs and the mRNAs
- They are recognized by specific enzymes and cut, so rRNAs and mRNAs are released
- The mitochondrial mRNAs do not carry cap at its 5’ end of the untranslated region
- Stop codons are completed by the addition of polyA tails

Extranuclear inheritance-Mitochondrial DNA (8/15)

Transcription Filling of stop codon



Extranuclear inheritance-Mitochondrial DNA (9/15)

Translation

- Existence of mitochondrial ribosomes
- Absence of 5' leader sequence
- Starting with f-Met
- Sensitivity to prokaryotic ribosomal function inhibitors (streptomycin, neomycin, chloramphenicol).
- There is not sensitivity in substances, in which the cytoplasmic ribosomes are sensitive, such as cycloheximide

Extranuclear inheritance- Mitochondrial DNA (10/15)

Translation

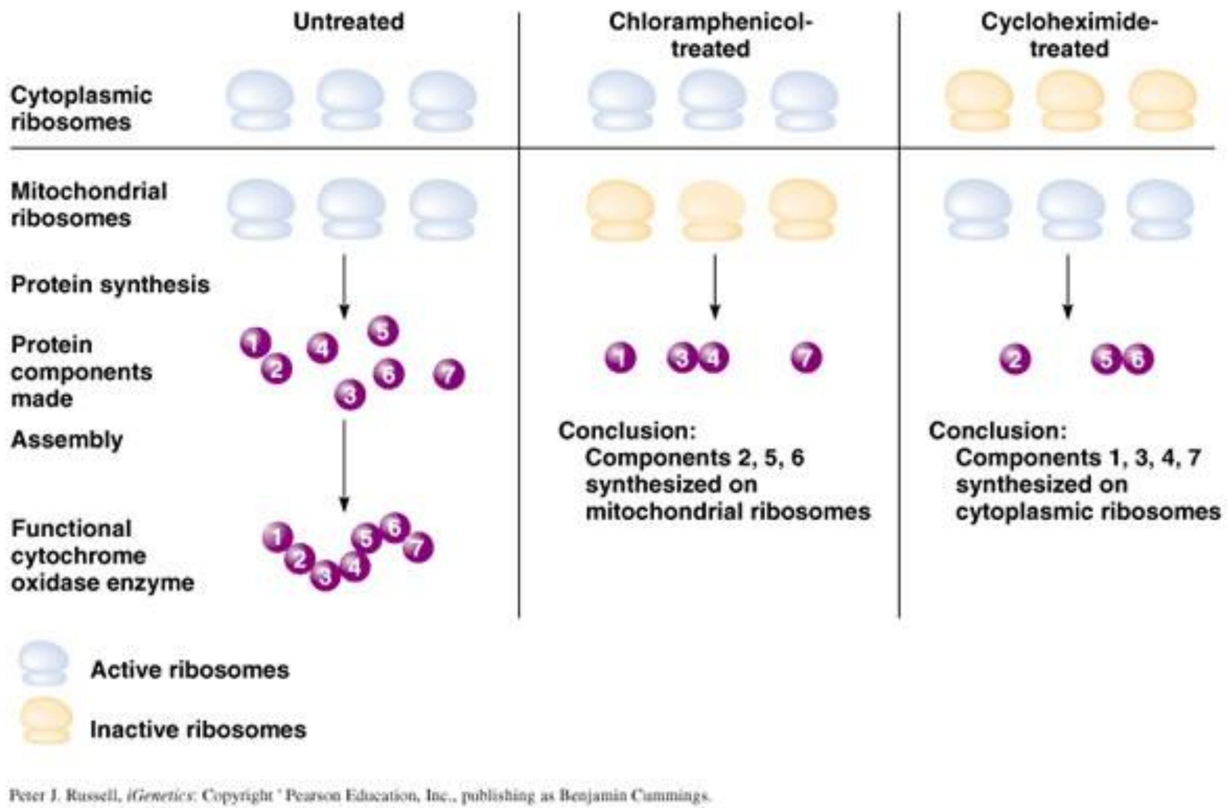


Figure 6: Some of the polypeptide subunits of cytochrome oxidase are synthesized from cytoplasmic ribosomes, while others are synthesized from mitochondrial ribosomes

Extranuclear inheritance-Mitochondrial DNA (11/15)

Translation

- Only the mitochondria of higher plants use the universal genetic code
- Mitochondria of other organisms use different genetic codes
- Different mitochondrial code for Ascites, Echinoderms, Yeasts

Extranuclear inheritance-Mitochondrial DNA (12/15)

Translation

Mitochondrial genetic code

	U	C	A	G	
U	UUU UUC } Phe UUA UUG } Leu	UCU UCC UCA UCG } Ser	UAU UAC } Tyr UAA Stop UAG Stop	UGU UGC } Cys UGA **Trp** UGG Trp	U C A G
C	CUU CUC CUA CUG } Leu	CCU CCC CCA CCG } Pro	CAU CAC } His CAA CAG } Gln	CGU CGC CGA CGG } Arg	U C A G
A	AUU **Met** AUC Ile AUA **Met** AUG Ile	ACU ACC ACA ACG } Thr	AAU AAC } Asn AAA AAG } Lys	AGU AGC } Ser AGA **Stop** AGG **Stop**	U C A G
G	GUU GUC GUA GUG } Val	GCU GCC GCA GCG } Ala	GAU GAC } Asp GAA GAG } Glu	GGU GGC GGA GGG } Gly	U C A G

Universal genetic code

	U	C	A	G	
U	UUU UUC } Phe UUA UUG } Leu	UCU UCC UCA UCG } Ser	UAU UAC } Tyr UAA Stop UAG Stop	UGU UGC } Cys UGA Stop UGG Trp	U C A G
C	CUU CUC CUA CUG } Leu	CCU CCC CCA CCG } Pro	CAU CAC } His CAA CAG } Gln	CGU CGC CGA CGG } Arg	U C A G
A	AUU AUC AUA } Ile AUG Met	ACU ACC ACA ACG } Thr	AAU AAC } Asn AAA AAG } Lys	AGU AGC } Ser AGA AGG } Arg	U C A G
G	GUU GUC GUA GUG } Val	GCU GCC GCA GCG } Ala	GAU GAC } Asp GAA GAG } Glu	GGU GGC GGA GGG } Gly	U C A G

Extranuclear inheritance- Mitochondrial DNA (13/15)

Translation of nuclear DNA

Wobble rules:

G	U/C
C	G
A	U
U	A/G

32 tRNAs

Translation of mtDNA

Simplified mating

14 tRNA recognize two codons that differ in the last nucleotide
8 tRNA recognize 4 codons

22 tRNAs

Extranuclear inheritance-Mitochondrial DNA (14/15)

Genetic/evolutionary studies

The mitochondrial DNA is an ideal genetic marker widely used in genetic and evolutionary studies because of the following features:

- ✓ Haploid nature
- ✓ Small size and conserved organization
- ✓ Easy extraction
- ✓ Absence of recombination
- ✓ Fast evolution pace
- ✓ Existence of regions with different evolution rates
- ✓ Existence of global primers
- ✓ Maternal inheritance

Extranuclear inheritance-Mitochondrial DNA (15/15)

Genetic/evolutionary studies

Mitochondrial DNA has been widely used in studies of human evolution

- Mitochondrial DNA polymorphisms track human migrations
Wallace, 2006, Sci. Amer., 277:40
- Mitochondrial genome variation and the origin of modern humans Ingman *et al*. 2000, Nature, **408**, 708-713
- Mitochondrial DNA and human evolution
Pakendorf and Stoneking 2005, Annu. Rev. Genomics Hum. Genet., 6:165–83

The data show that all people come from a small group of Africans who appeared about 200,000 years ago.

Extranuclear inheritance

Chloroplastic DNA

1986: Publication of primary structure of cpDNA of a bryophyte and tobacco

Bryophyte: 121024 bp
Tobacco: 155844bp

- The typical size of the chloroplast is 120-220 kb
- Includes 4 regions (LSC, SSC, IRa & IRb)
- The typical number of genes is approximately 140
- Existence of spacer DNA and introns

Extranuclear inheritance-Chloroplastic DNA (1/2)

- Includes 4 rRNA genes (16S, 23S, 4.5S, 5S) (2X), 30-32 tRNAs, 90 protein genes, 20 of which are related to the photosynthesis and electron transport
- The replication mechanism of cpDNA is similar to that of mtDNA
- The protein composition is similar to prokaryotes but ribosomes differ from mitochondrial and prokaryotic
- <u>Universal genetic code</u>
- Sensitivity to antibiotics and inhibitors same to mitochondria
- 2/3 of chloroplast proteins are coded by the nuclear DNA

Extranuclear inheritance-Chloroplastic DNA (2/2)

Similarities to prokaryotic organization:

- Grouped genes
- Synchronous transcription of functionally similar genes
- Gene series similar to *E. coli* (e.g. ribosomal protein genes)
- Sensitivity to antibiotics and inhibitors of protein synthesis in prokaryotes

Extranuclear inheritance-Origin of mitochondria and chloroplasts (1/6)

Endosymbiotic theory

Symbiosis of eukaryotic cell with a bacterium

⇓

mitochondria

Parallel or subsequent symbiosis with a cyanobacterium

⇓

chloroplasts

Extranuclear inheritance-Origin of mitochondria and chloroplasts (2/6)

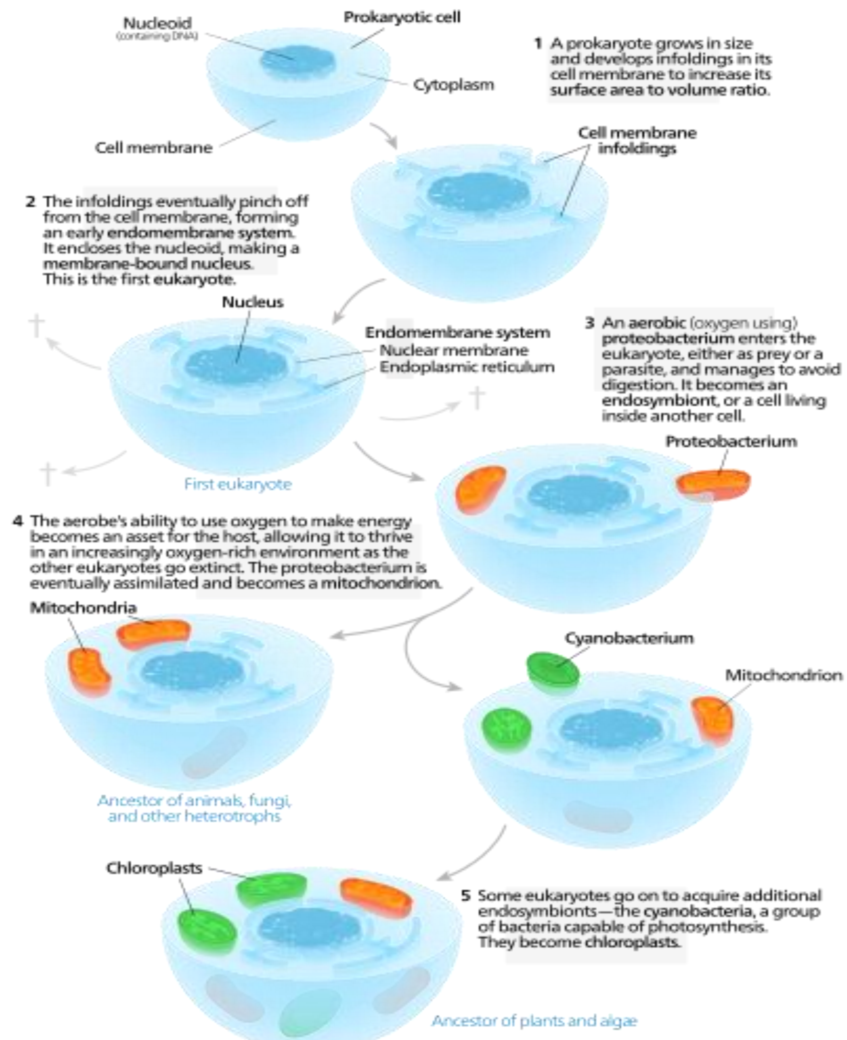


Figure 7: Endosymbiotic theory

Extranuclear inheritance-Origin of mitochondria and chloroplasts (3/6)

Data that support the theory of endosymbiosis:

- Circular and free genome
- Absence of organization in chromosomes
- Genes similar to bacterial
- Independent system of replication, transcription and translation

Extranuclear inheritance-Origin of mitochondria and chloroplasts (4/6)

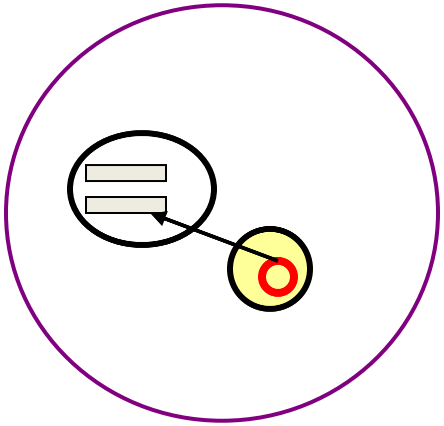
A small "problem"…

- The smallest genome of free organism
- *Mycoplasma genitalium*
  - 580 kB, 470 genes

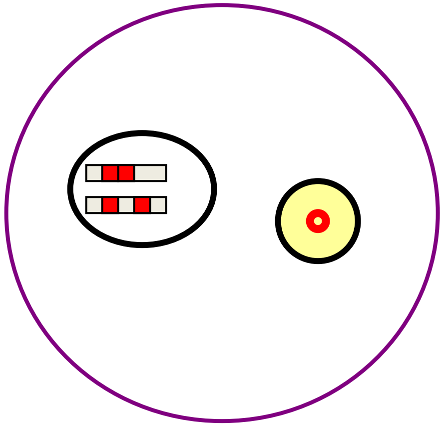
- What happened to the other "mitochondrial" genes?

Extranuclear inheritance-Origin of mitochondria and chloroplasts (5/6)

Transfer of mtDNA and cpDNA to the nucleus



Early eukaryote



Modern eukaryote

Cooperation of nucleus and mitochondria - chloroplasts

RUBISCO the most common protein in the world:
8rbcL (chloroplasts) / 8rbcs (nucleus)

Extranuclear inheritance-Origin of mitochondria and chloroplasts (6/6)

The genome of organelles shows a significant difference from prokaryotes:

The presence of introns

Did the introns exist before the prokaryote-eukaryote diversification?

- Were the chloroplast introns created from genetic material rearrangements?

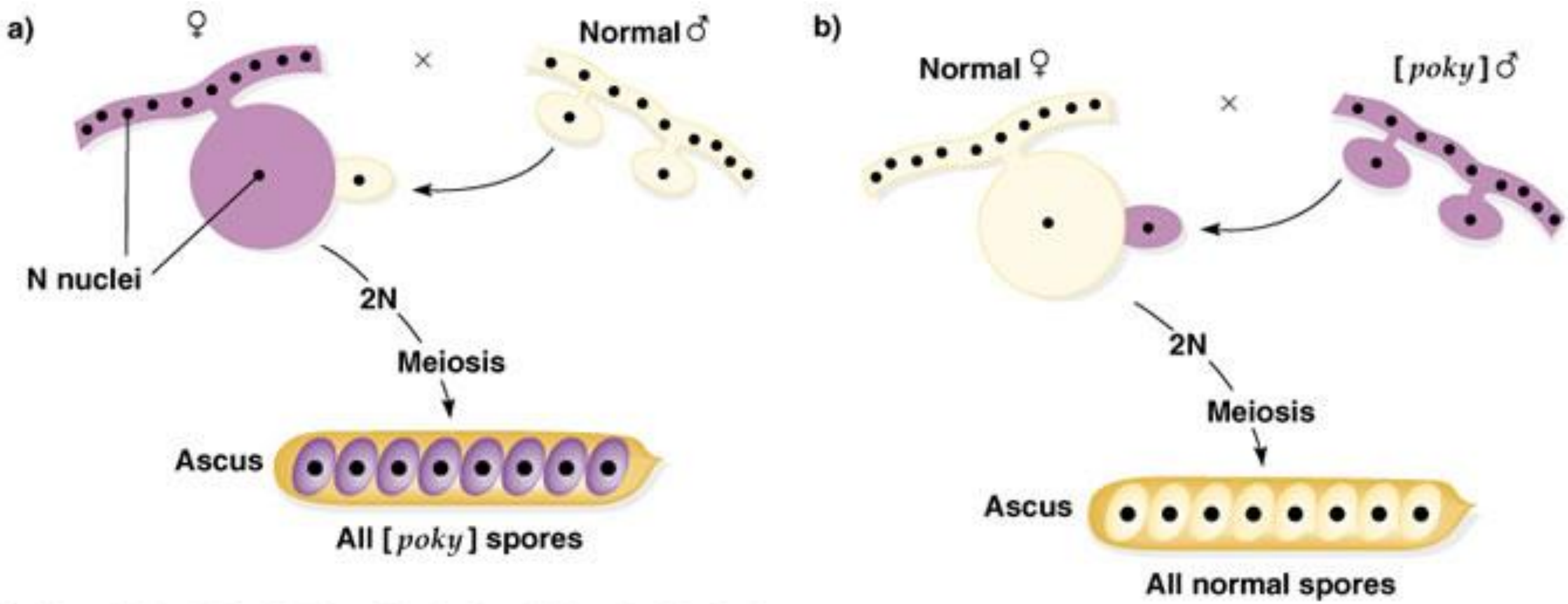
Extranuclear inheritance-Criteria

- The typical Mendelian ratios of separation are not followed (no meiotic separation)
- In multicellular organisms there are differences to the descendants coming from inverse intersections (maternal inheritance)
- Not possible mapping in nuclear linkage groups
- The characteristics remain even when the nucleus is replaced
- Mutagens of nuclear genes do not affect genes organelles

Extranuclear inheritance-Examples (1/6)

Poky mutants in *Neurospora*

Figure 8: Results of mutual crossings in Neurospora between a strain (poky) and wild type



Extranuclear inheritance-Examples (2/6)

Poky mutants in *Neurospora*

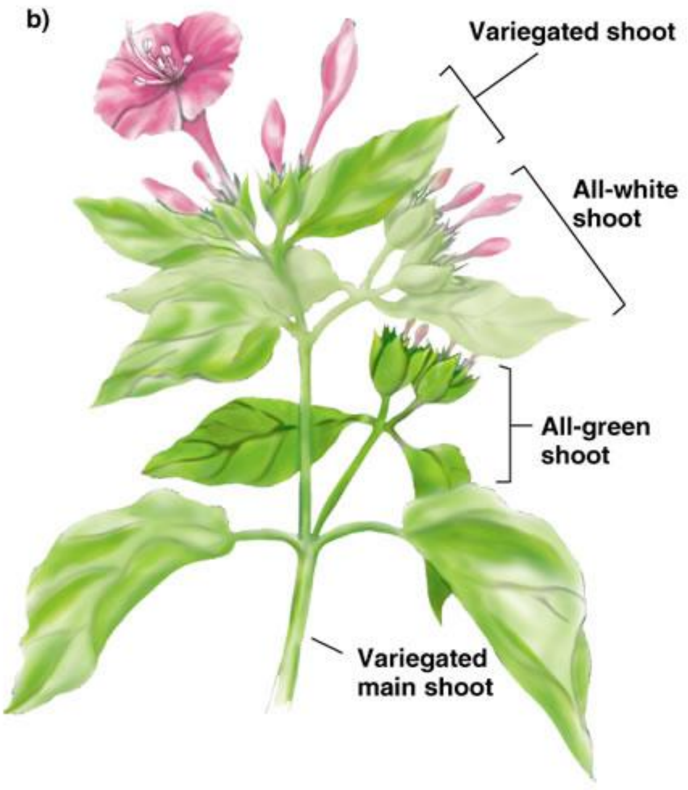
The mutant phenotype of slow growth (poky) in *Neurospora crassa* shows maternal inheritance

At a molecular level, the mutation (poky) is a deficit in the promoter of mitochondrial rRNA gene of the small ribosomal subunit, leading to reduced ability of protein synthesis and the slow growth phenotype

Extranuclear inheritance-Examples (3/6)

Inheritance of chloroplasts in evening primrose *Mirabilis jalapa*

Figure 9



Normal chloroplasts
Green photosynthetic

Mutant chloroplasts
White non-photosynthetic

Mixed chloroplasts
White / green

Extranuclear inheritance-Examples (4/6)

Inheritance of chloroplasts in evening primrose *Mirabilis jalapa*

Crossing results

Maternal inheritance

The color of the chloroplast is determined by a cp gene

Strain of female parent	Strain of male parent	descendents
white	White	white
	green	White
	multicolored	White
green	White	Green
	Green	Green
	Multicolored	green
multicolored	White	multicolored, white or green
	green	multicolored, white or green
	multicolored	multicolored, white or green

Extranuclear inheritance-Examples (5/6)

Inheritance of chloroplasts in evening primrose *Mirabilis jalapa*

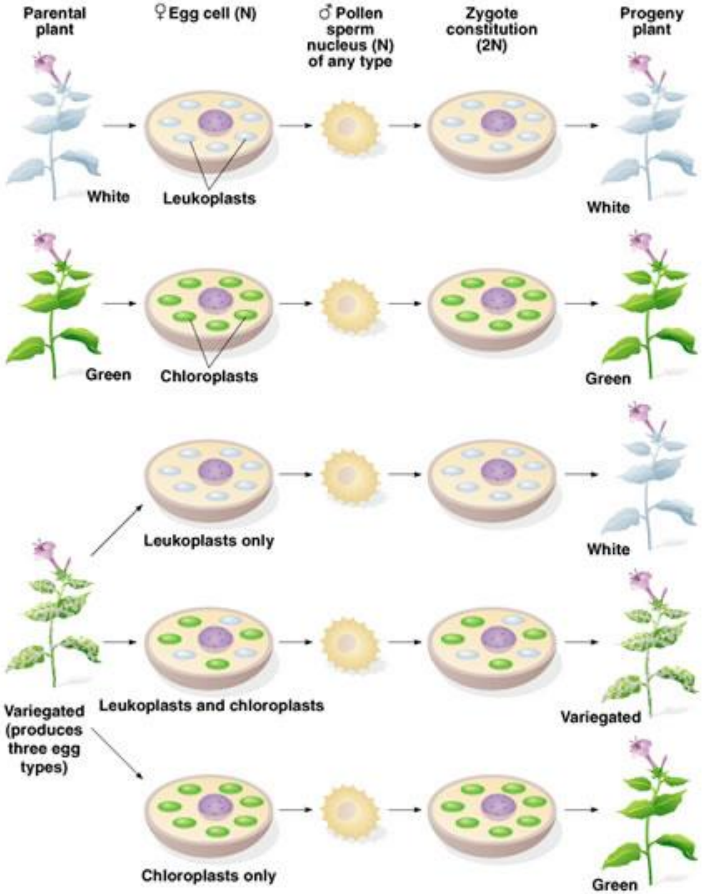
<u>Shoot color</u>

White

Green

Multicoloured

Figure 10: The inheritance of the color of the shoot in the evening primrose



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Extranuclear inheritance-Examples (6/6)

Inheritance of chloroplasts in evening primrose *Mirabilis jalapa*

Random separation of normal and mutant cpDNA during the division of chloroplasts

- Chloroplasts
- Leucoplasts

Random separation of chloroplasts and leucoplasts during cell division

- White phenotype
- Green phenotype

HETEROPLASMY

Extranuclear inheritance- Exclusions to Maternal inheritance

Maternal inheritance of mtDNA & the cpDNA has proven to most organisms

Exclusions:

✓ In conifers the cpDNA is inherited paternally, while in some angiosperms inherited from the two parents

✓ In yeast the mtDNA is inherited from the two parents

✓In the female mussels the mtDNA is inherited from the mother, while in males from both parents

✓Presence of paternal mtDNA in mice at frequency 10^{-4}

Extranuclear inheritance-Mitochondial diseases (1/2)

Mutagenicity rate 10 times higher

Several diseases caused by mitochondrial gene mutations

www.mitomap.org

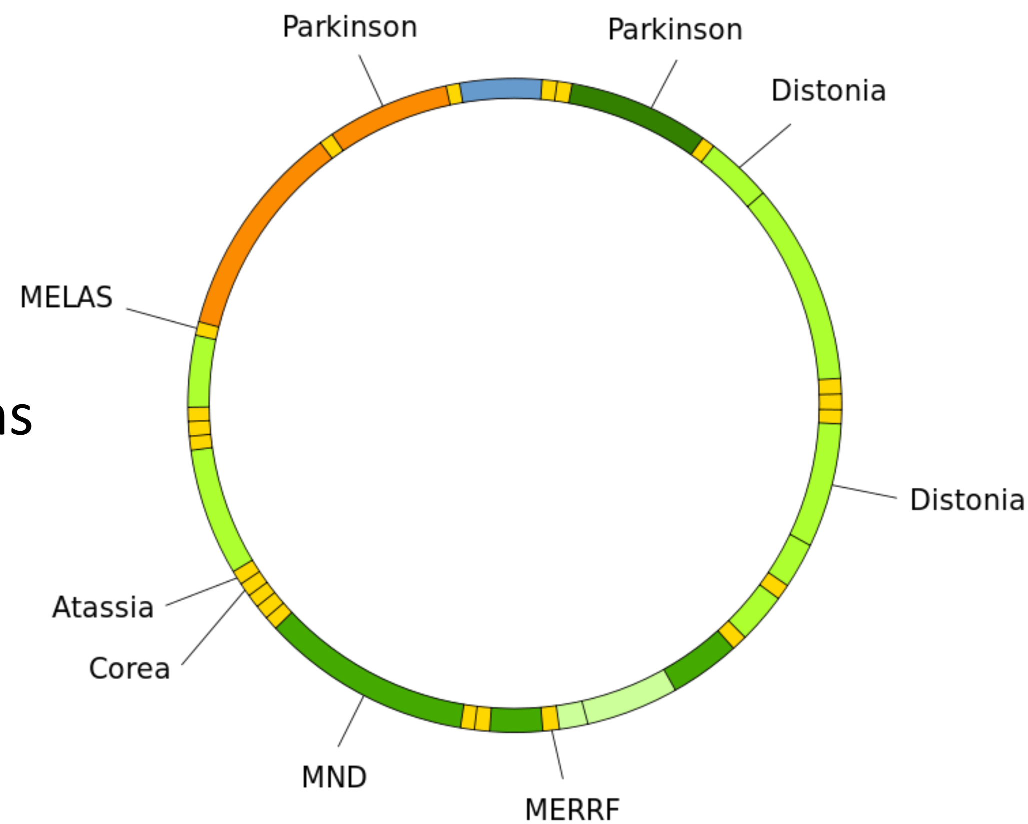


Figure 11: Mitochondrial DNA and diseases

Extranuclear inheritance-Mitochondial diseases (2/2)

Mitochondrial cytopathies: affects the muscles and nerves

Leber optical neuropathy (LHON): total or partial blindness, mutation in proteins of electron transfer

Kearns –Sayre Syndrome: neuromuscular problems, paralysis of optical muscle, heart disease, retinal degeneration, deficits involving tRNA genes

Myoclonic epilepsy (MERRF): convulsions and ataxia, abnormal mitochodrion morphology, nucleotide change in the tRNA lysine

Epigenetic inheritance (1/4)

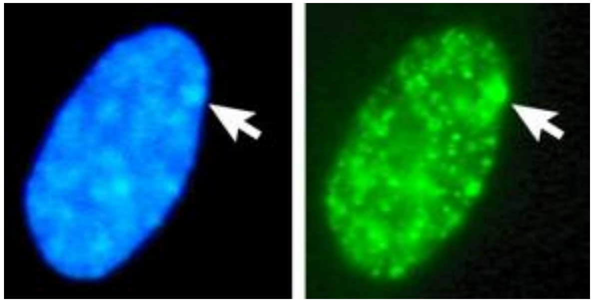
Inherited pattern caused by modification of nuclear genes, which causes changes in their expression but not in their structure

- The epigenetic changes do not remain in different generations
- The epigenetic changes may be caused by modifications of sequences or whole chromosomes
- May occur during ovulation, spermatogenesis or early developmental stages

Epigenetic inheritance (2/4)

Gene dose compensation

- Sex mammalian chromosomes
- Disable X chromosome



Barr body

Εικόνα 12: Barr Body

- Heterozygous females for sex-linked genes show mosaic phenotype

Epigenetic inheritance (3/4)

Genomic imprinting

- Phenomenon in which the expression of a gene depends on whether it is inherited from the female or male parent
- Depending on the "sign - imprint" of each gene, the progeny express either the maternal or the paternal alleles but <u>NOT both</u>
  - Monoallelic expression

Epigenetic inheritance (4/4)

- The imprint is permanent in somatic cells
- It may concern:
  - Unique gene
  - Part of chromosome
  - Whole chromosome
- Syndromes in cases of chromosomal abnormalities or inheriting a pair of chromosomes from the same parent (uniparental disomy)

Infectious inheritance

Extranuclear inheritance which is not due to the genetic material of organelles but to infectious agents (bacteria, viruses)

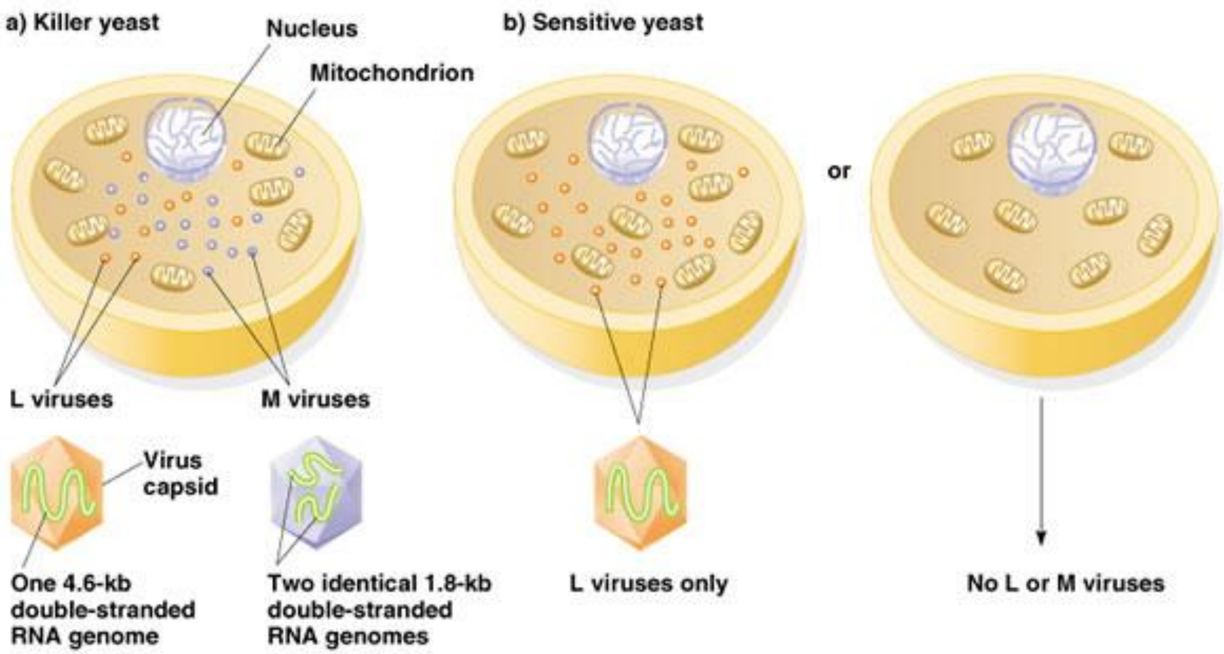


Figure 13: Infectious inheritance in yeast

Maternal effect (1/2)

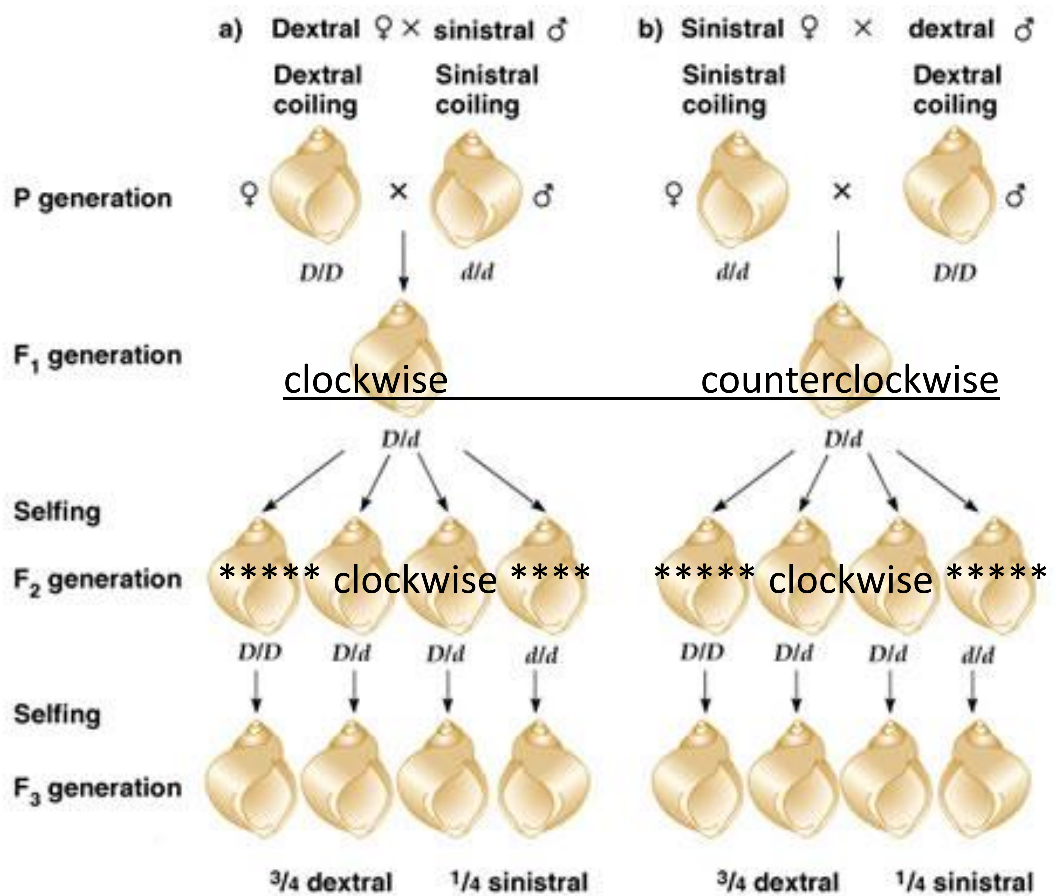
Figure 14: The snail *Limnaea peregra*

Phenotype of an offspring is determined by the nuclear genotype of its mother

No involvement of extranuclear genes

Maternal effect (2/2)

Figure 15: Inheritance of coiling in *Limnaea* snails



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