

# Extranuclear Inheritance

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# Terms Defined

**Cytoplasmic inheritance**- Transmission of heredity traits through factors in the cytoplasm.

**Uniparental inheritance**- Transmission of heredity traits through only one parent.

- **maternal inheritance**- Uniparental transmission of heredity traits through the mother.

- **paternal inheritance**- Uniparental transmission of heredity traits through the father.

# Extranuclear inheritance

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- Extranuclear inheritance refers to inheritance patterns involving **genetic material outside the nucleus**
- The two most important examples are due to genetic material within organelles **Mitochondria and chloroplasts**
- These organelles are found in the cytoplasm
- Therefore, extranuclear inheritance is also termed cytoplasmic inheritance
- **EXTRANUCLEAR INHERITANCE**

# NON-MENDELIAN INHERITANCE

## INTRODUCTION

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- Mendelian inheritance patterns involve genes that
- Directly influence the outcome of an organism's traits and Obey Mendel's laws
- Most genes in eukaryotic species follow a Mendelian pattern of inheritance
- However, there are many that don't
- Indeed, linkage which we considered in the last two lectures follows non-Mendelian inheritance

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- Additional patterns of inheritance that deviate from a Mendelian pattern include:
    - ✓ Maternal effect and epigenetic inheritance
    - ✓ Involve genes in the nucleus
    - ✓ Extranuclear inheritance
  - Involves genes in organelles other than the nucleus
    - 1. Mitochondria
    - 2. Chloroplasts
    - 3. plasmid

- ❑ Maternal effect refers to an inheritance pattern for certain nuclear genes in which the genotype of the mother directly determines the phenotype of her offspring
- ❑ Surprisingly, the genotypes of the father and offspring themselves do not affect the phenotype of the offspring
- ❑ This phenomenon is due to the accumulation of gene products that the mother provides to her developing eggs
- **The phenotype of the progeny is determined by the mother's genotype NOT phenotype**
- The genotypes of the father and offspring do not affect the phenotype of the offspring

# MATERNAL EFFECT

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- **Epigenetic inheritance refers to a pattern in which a modification occurs to a nuclear gene or chromosome that alters gene expression**
- However, the expression is not permanently changed over the course of many generations
- Epigenetic changes are caused by DNA and chromosomal modifications
- These can occur during oogenesis, spermatogenesis or early embryonic development

# EPIGENETIC INHERITANCE

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- The purpose of dosage compensation is to offset differences in the number of active sex chromosomes
- Dosage compensation has been studied extensively in mammals, *Drosophila* and *Caenorhabditis elegans*
- Depending on the species, dosage compensation occurs via different mechanisms

# Dosage Compensation

## Mechanisms of Dosage Compensation Among Different Species

Species	Sex Chromosomes in:		Mechanism of Compensation
	Females	Males	
Placental mammals	XX	XY	One of the X chromosomes in the somatic cells of females is inactivated. In certain species, the paternal X chromosome is inactivated while in other species, such as humans, either the maternal or paternal X chromosome is randomly inactivated throughout the female's body.
Marsupial mammals	XX	XY	The paternally derived X chromosome is inactivated in the somatic cells of females.
<i>Drosophila melanogaster</i>	XX	XY	The level of expression of genes on the X chromosome in males is increased 2-fold.
<i>Caenorhabditis elegans</i>	XX*	X0	The level of expression of genes on both X chromosomes in hermaphrodites is decreased to 50% levels compared to males.

\*In *C. elegans*, an XX individual is a hermaphrodite, not a female.

# The mechanism of X inactivation is also known as the Lyon hypothesis

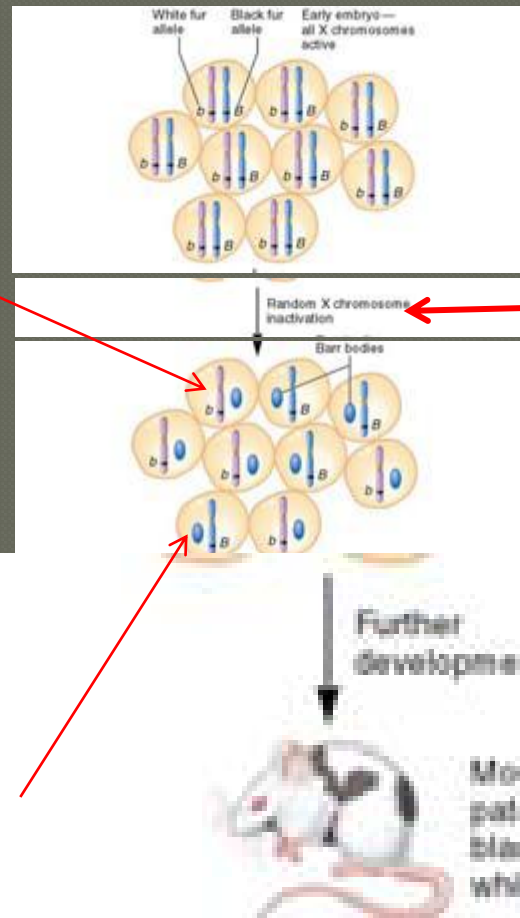
- The example involves a white and black variegated coat color found in certain strains of mice
- A female mouse has inherited two X chromosomes
  1. One from its mother that carries an allele conferring white coat color ( $X^b$ )
  2. One from its father that carries an allele conferring black coat color ( $X^B$ )



Mouse with patches of black and white fur

The epithelial cells derived from this embryonic cell will produce a patch of white fur

While those from this will produce a patch of black fur



At an early stage of embryonic development

# EXTRANUCLEAR INHERITANCE

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- Extranuclear inheritance refers to inheritance patterns involving genetic material outside the nucleus
- The two most important examples are due to genetic material within organelles Mitochondria and chloroplasts
- These organelles are found in the cytoplasm
- Therefore, extranuclear inheritance is also termed cytoplasmic inheritance

# Types of Extranuclear Inheritance

- **Organelle Heredity**

  - Mitochondria

  - Chloroplast

- **Infectious Heredity**

- **Maternal Effect**

- **Genomic Imprinting**

# Maternal effects

Maternal effects occur when the mother's genotype or phenotype affects the phenotype of her progeny directly.

For example, older salmon produce larger eggs which have more nutrients so that their fry are larger at hatching.



# Maternal effects and maternal inheritance

- ❖ *Mothers can affect offspring phenotype in lots of ways in addition to normal Mendelian inheritance of her alleles at nuclear genes*
- ❖ Environmental maternal effects
- ❖ Imprinting/epigenetics
- ❖ Genetic maternal effects
- ❖ Maternal inheritance of mitochondrial & chloroplast genes

## Genetic Composition of Mitochondria and Chloroplasts

Species	Organelle	Nucleoids per Organelle	Total Number of Chromosomes per Organelle
<i>Tetrahymena</i>	Mitochondrion	1	6–8
Mouse	Mitochondrion	1–3	5–6
<i>Chlamydomonas</i>	Chloroplast	5–6	~80
Euglena	Chloroplast	20–34	100–300
Higher plants	Chloroplast	12–25	~60

Data from: Gillham, N. W. (1994). *Organelle Genes and Genomes*. Oxford University Press, New York.

# Genetic maternal effects

- ❖ Genes are inherited normally, but trait is controlled by mother's genotype
- ❖ Maternal effect occurs when the offspring phenotype is directly determined by mother's genotype (not indirectly via offspring genotype)

## Genetic maternal effects -- Coiling in the snail *Limnea peregra*

The direction of shell coiling is controlled by a single gene.

Right (dextral) coiling (*D*) is dominant to left (sinistral) coiling (*d*).

The phenotype of an individual is determined by the genotype of its mother. The genotype of a mother determines the structure of the eggs that she produces.

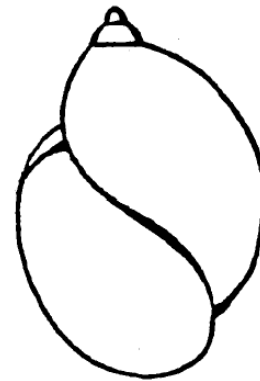
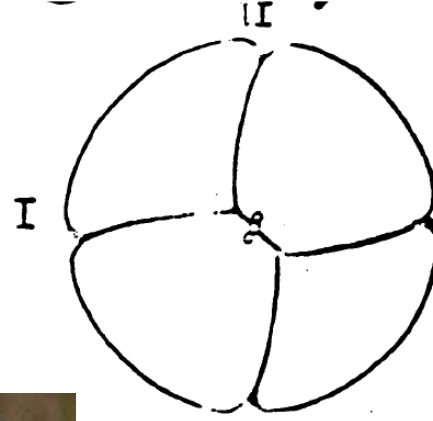
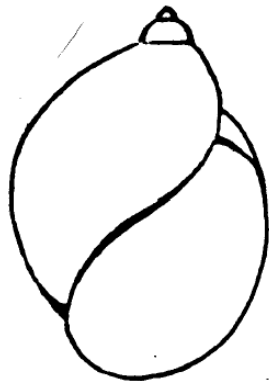
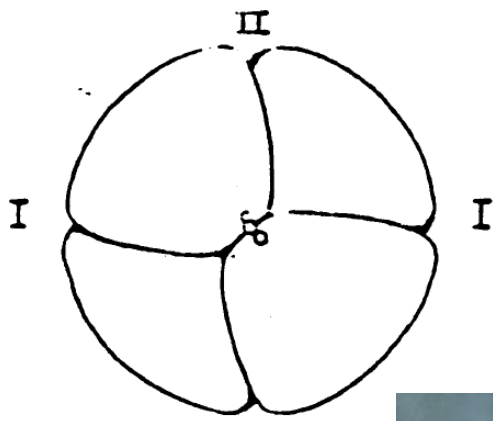


Maternal  
genotype

*DD*

*Dd*

Right  
(dextral  
)



Maternal  
genotype

*dd*

Left  
(sinistral)

Progeny = *DD*, *Dd*, or *dd*

# Maternal Effect: shell coiling in snails

Uniparental inheritance

DD and Dd mothers  
right-handed offspring

dd mothers  
left-handed offspring

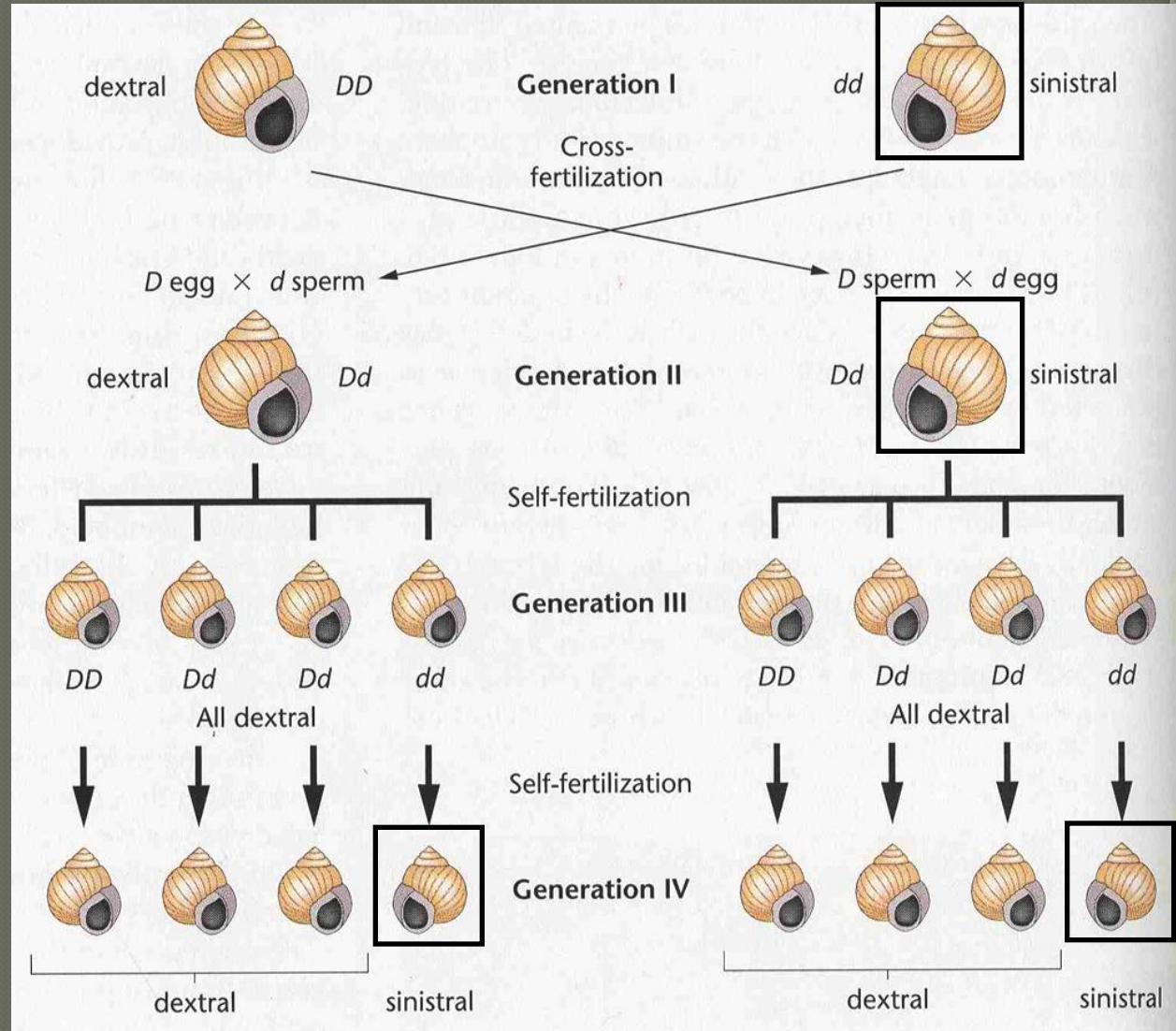
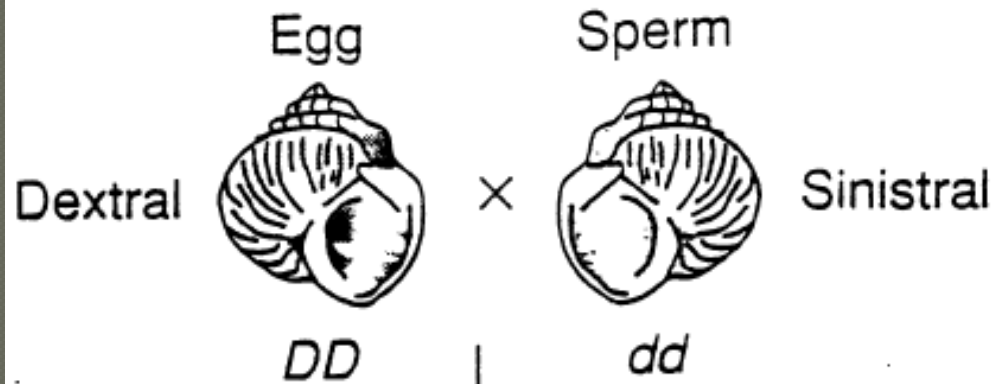


Fig. 8.9

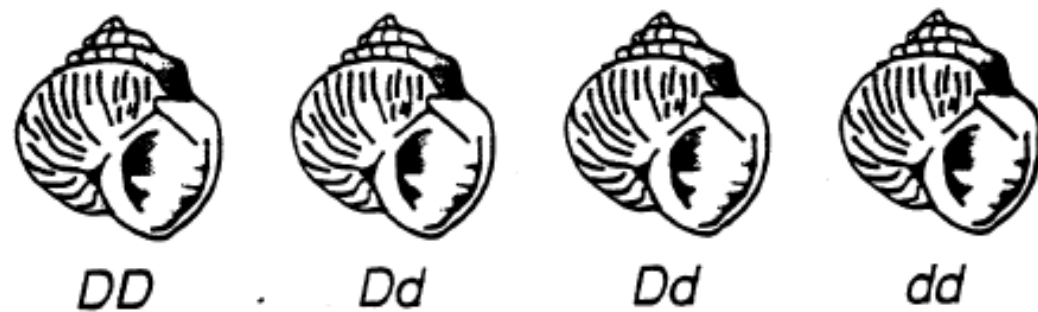
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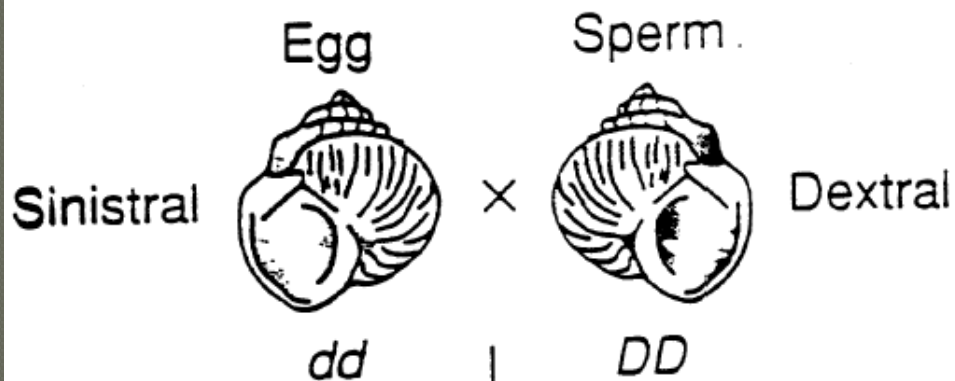
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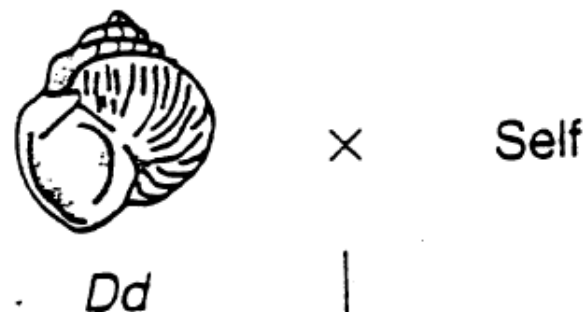
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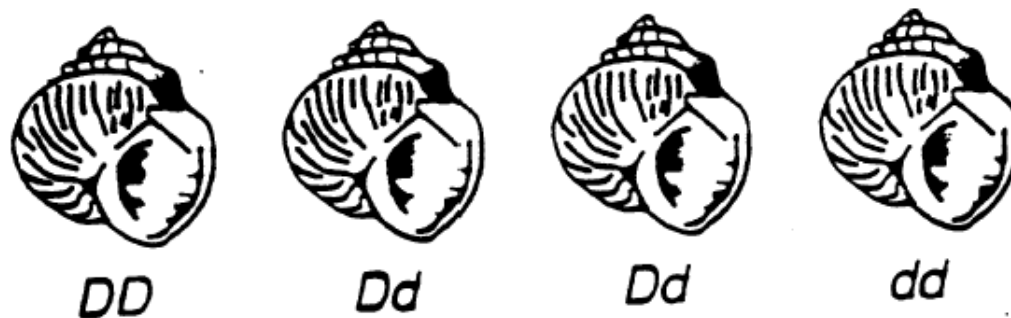
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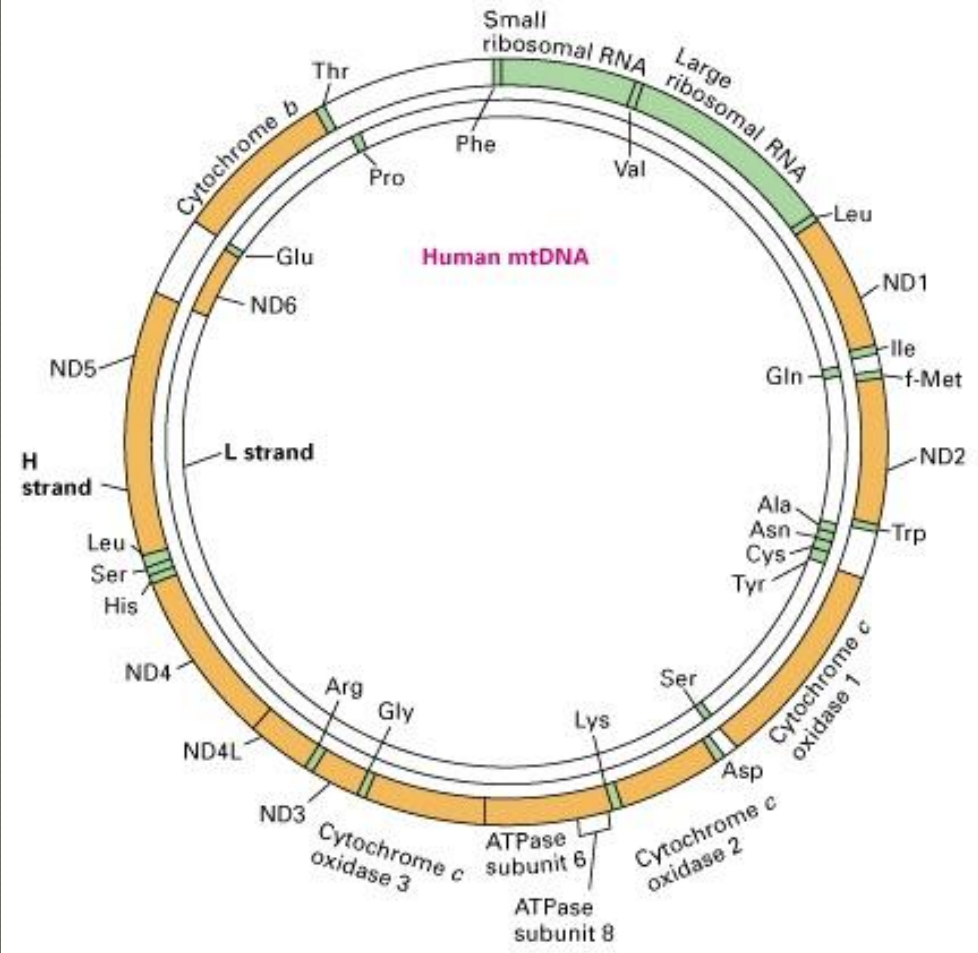
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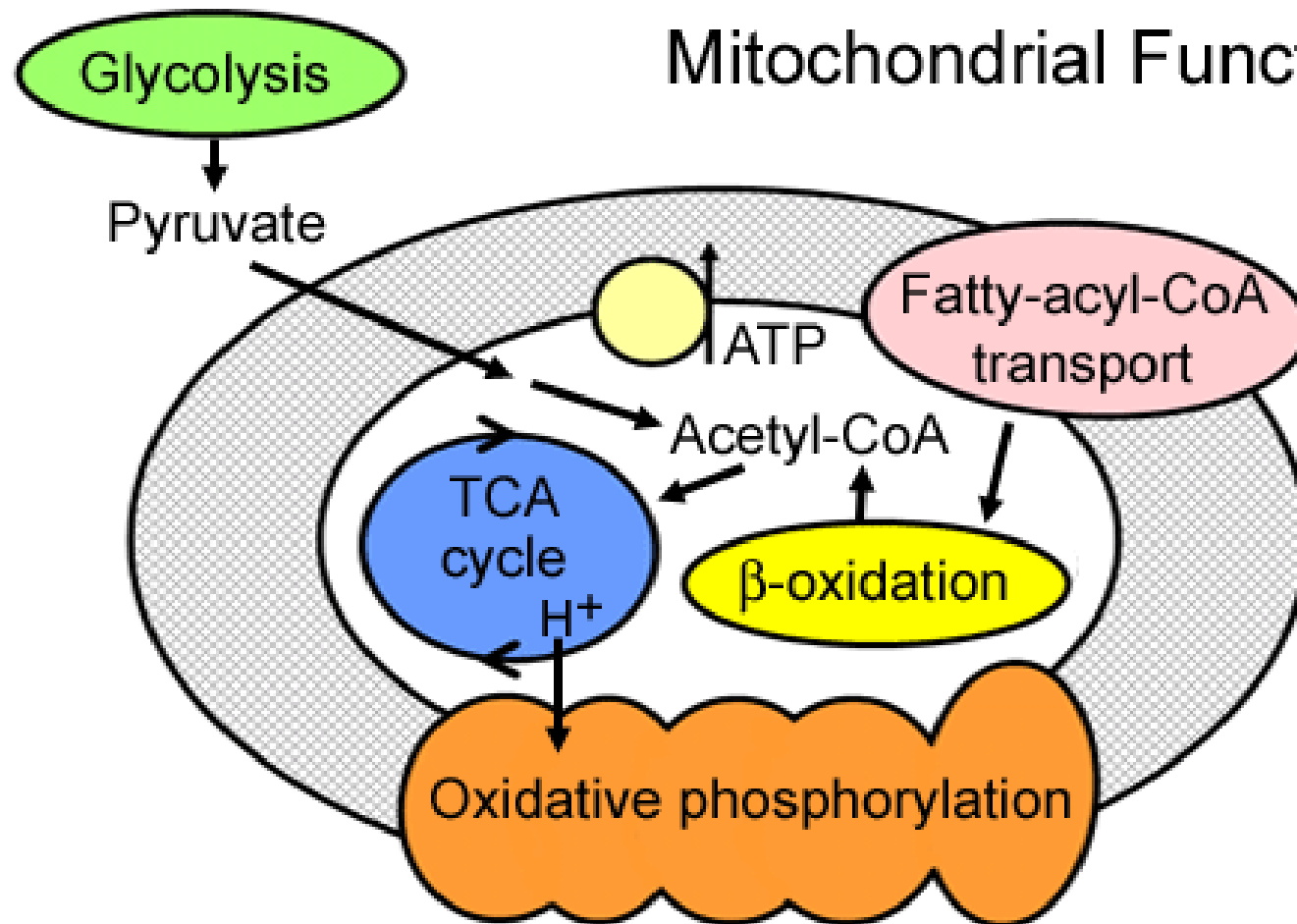


**Mitochondrial DNA in humans encodes just 13 genes - all are necessary for oxidative phosphorylation (OXPHOS)**



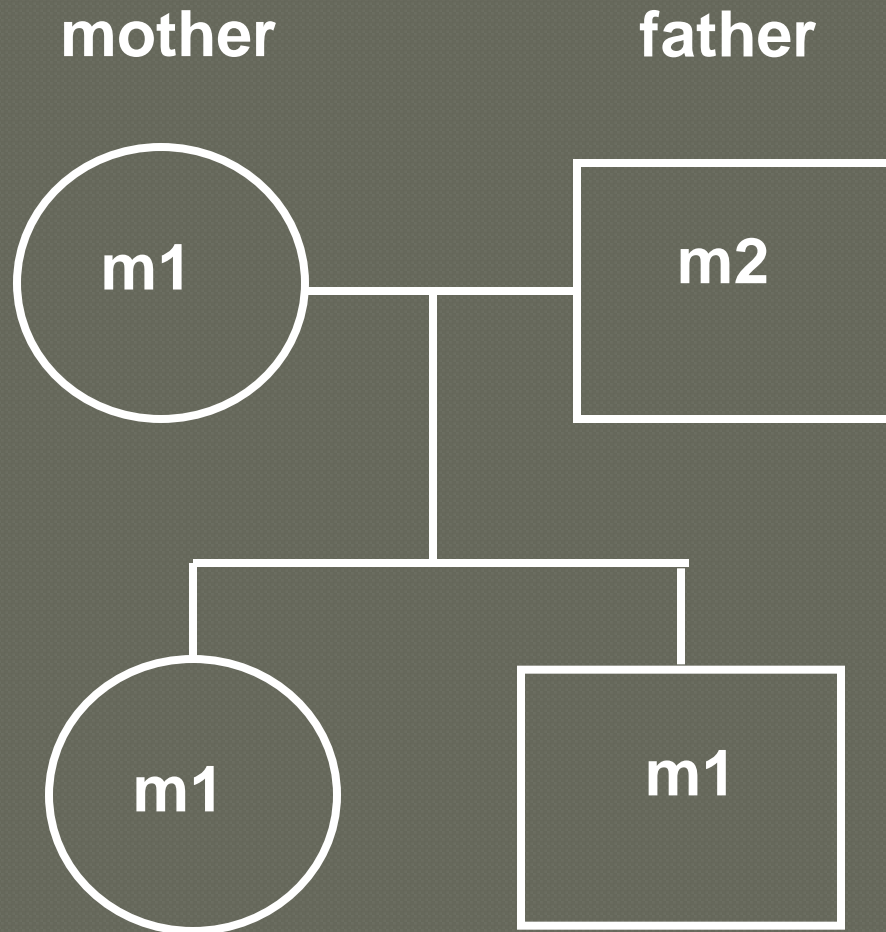
- Haploid, circular DNA molecule (derived from bacterial endosymbiont)
- Reproduces via mitosis (many mt per cell)
- Little or no recombination

# Mitochondrial Functions



# All children inherit their mother's mtDNA type

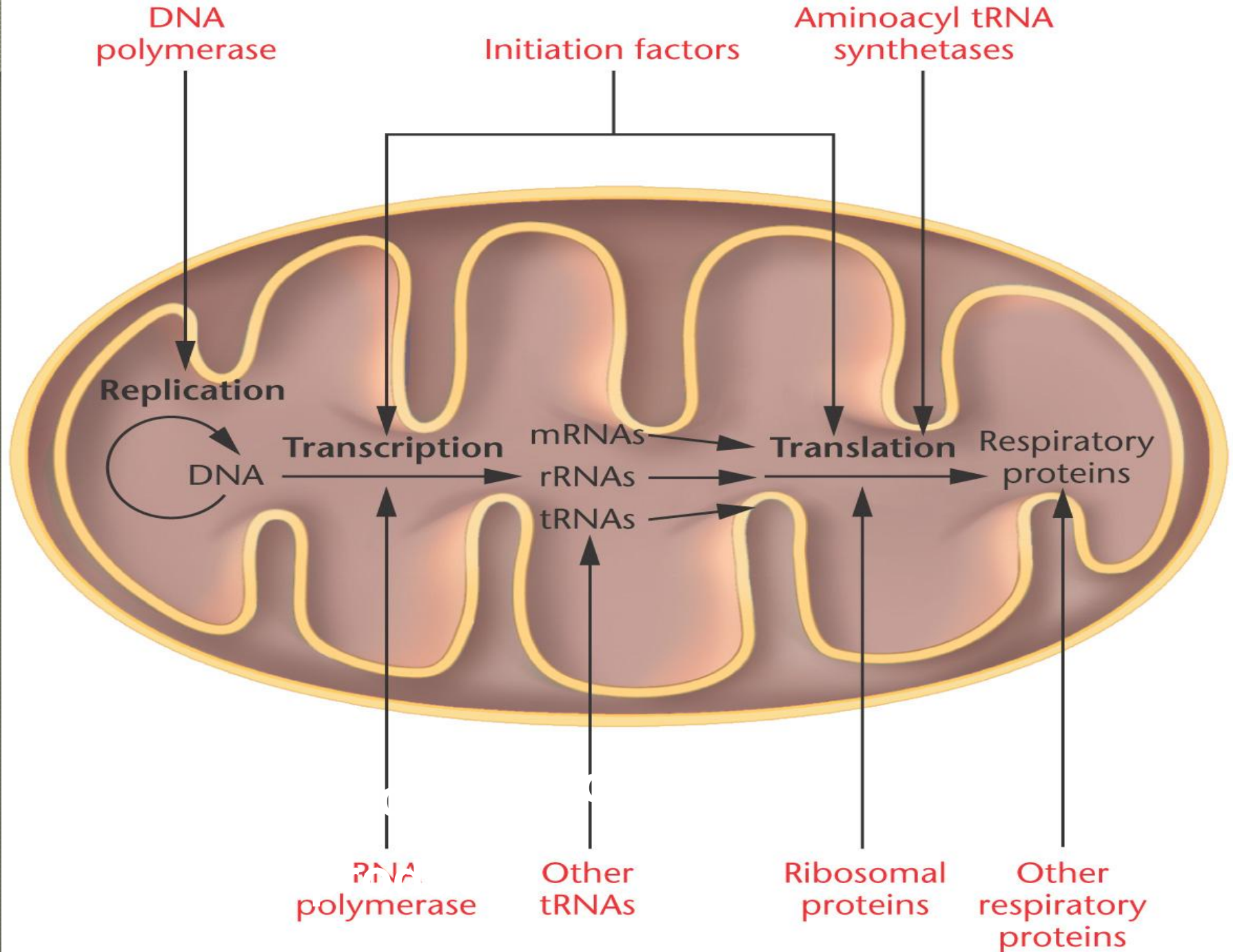
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# Mitochondrial Genes/Expression

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- ◉ Protein synthetic apparatus combination of mtDNA and nuclear-encoded
  - But nuclear-encoded proteins distinct from their cytoplasmic or nuclear counterparts
    - RNAP is single polypeptide and is inhibited by rifampicin/rifamycin
  - But sensitive to antibiotics targeted normally against prokaryotes
  - Ribosomes range from 55-80S



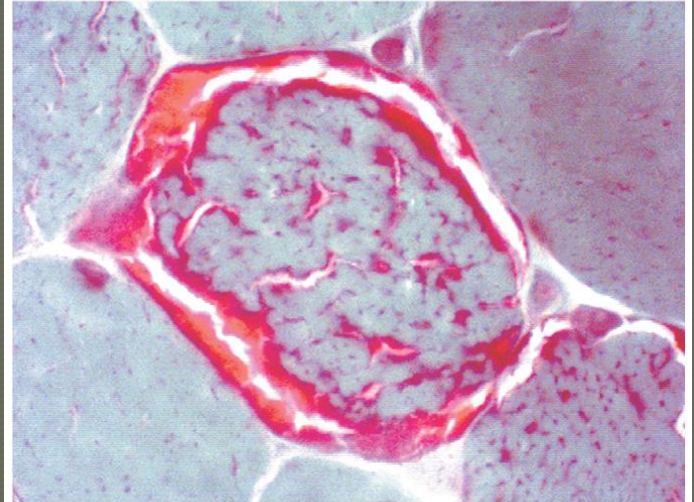
# mtDNA Mutations and Human Genetic Disorders

- Human mtDNA is 16,569 bp
  - Encodes 13 proteins, 22 tRNAs and 2 rRNAs
- Heteroplasmy
  - Variable mixture of genetically distinct mitochondria/mtDNAs
- Properties of mtDNA-encoded traits
  - Maternal inheritance pattern
  - Deficiency in bioenergetic function of organelle
  - Specific mutation in an mtDNA gene

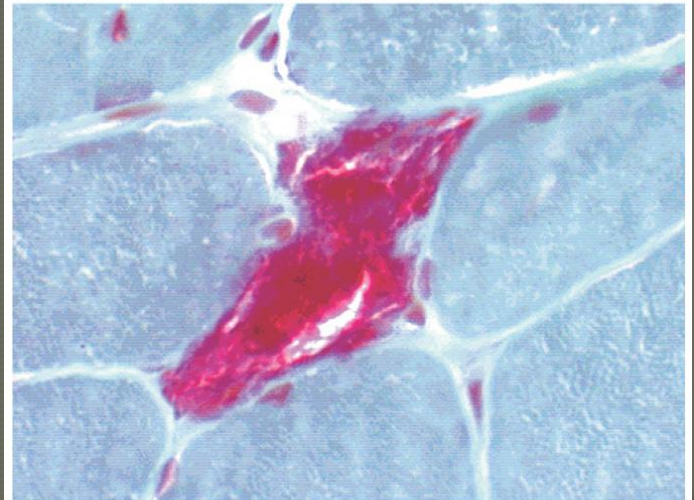
# Human mtDNA Disorders

- Myoclonic epilepsy and ragged red fiber disease (MERRF)
  - Fibers from proliferation of aberrant mitochondria
  - Mutation in mtDNA tRNA gene

(a)



(b)



# In humans, mitochondrial variation influences male fertility..

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*Am. J. Hum. Genet.* 67:682–696, 2000

## **Human mtDNA Haplogroups Associated with High or Reduced Spermatozoa Motility**

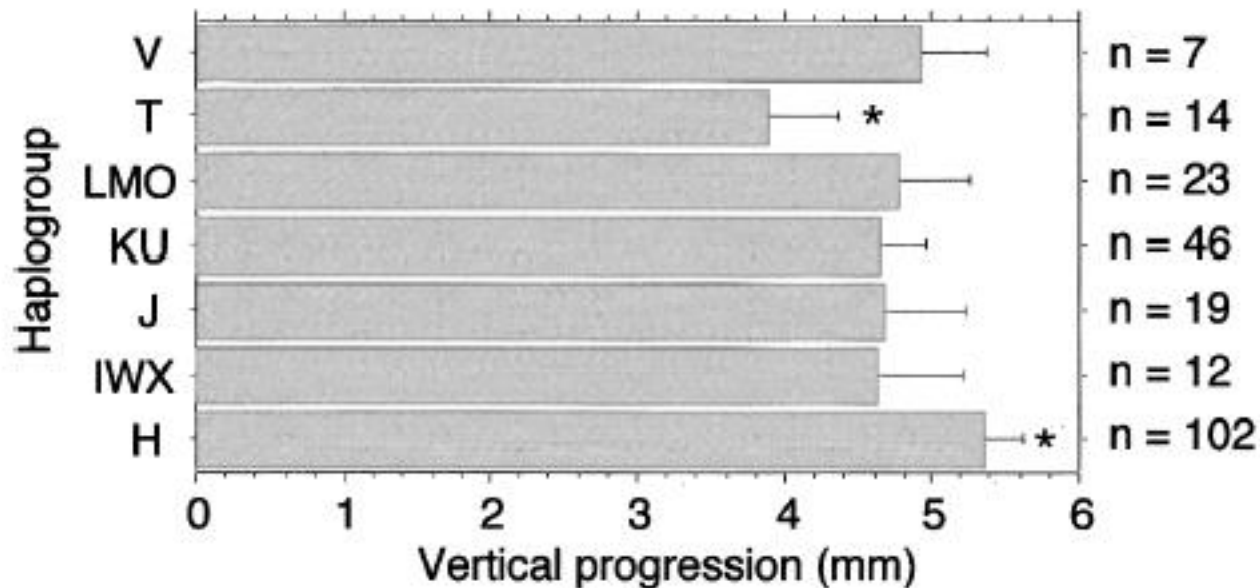
Eduardo Ruiz-Pesini,<sup>1</sup> Ana-Cristina Lapeña,<sup>1</sup> Carmen Díez-Sánchez,<sup>1</sup> Acisclo Pérez-Martos,<sup>1</sup> Julio Montoya,<sup>1</sup> Enrique Alvarez,<sup>2</sup> Miguel Díaz,<sup>3</sup> Antonio Urriés,<sup>4</sup> Luis Montoro,<sup>5</sup> Manuel J. López-Pérez,<sup>1</sup> and José A. Enríquez<sup>1</sup>

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A variety of mtDNA mutations responsible for human diseases have been associated with molecular defects in the OXPHOS system. It has been proposed that mtDNA genetic alterations can also be responsible for sperm dysfunction. In addition, it was suggested that if sperm dysfunction is the main phenotypic consequence, these mutations could be fixed as stable mtDNA variants, because mtDNA is maternally inherited. To test this possibility, we have performed an extensive analysis of the distribution of mtDNA haplogroups in white men having fertility problems. We have found that asthenozoospermia, but not oligozoospermia, is associated with mtDNA haplogroups in whites. Thus, haplogroups H and T are significantly more abundant in nonasthenozoospermic and asthenozoospermic populations, respectively, and show significant differences in their OXPHOS performance.

# In humans, mitochondrial variation influences male fertility..

Sperm races: H haplotype best, T haplotype worst



# Organelle Heredity (chloroplast)

*Chlamydomonas reinhardtii* and drug resistance:

## Life cycle



$\text{mt}^+$  passes on **chloroplast** genetic material.

$\text{mt}^-$  passes on **mitochondria** genetic material.

$\text{str}^R \text{mt}^+ \times \text{str}^S \text{mt}^-$



$\frac{1}{2} \text{mt}^+ \quad \frac{1}{2} \text{mt}^-$

100%  $\text{str}^R$

$\text{str}^S \text{mt}^+ \times \text{str}^R \text{mt}^-$



$\frac{1}{2} \text{mt}^+ \quad \frac{1}{2} \text{mt}^-$

100%  $\text{str}^S$

Streptomycin resistance is inherited through the chloroplast.

# *Saccharomyces petite* Mutations

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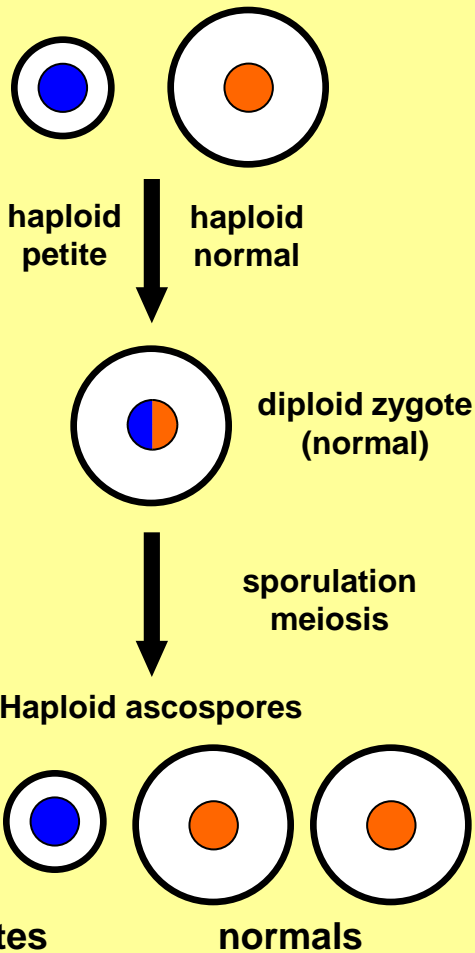
- ◉ *petite* mutations give rise to small colonies
  - Aerobic respiration blocked
  - Live anaerobically
    - *S. cerevisiae* is a facultative anaerobe
- ◉ Two types
  - **Segregational petites** encoded by nuclear genes showing Mendelian inheritance
  - cytoplasmic transmission pattern petites
    - Neutral petites demonstrate (give all wt offspring when crossed to wt)
    - Suppressive petites (behave like poky in *Neurospora*)

# Organelle Heredity (mitochondria)

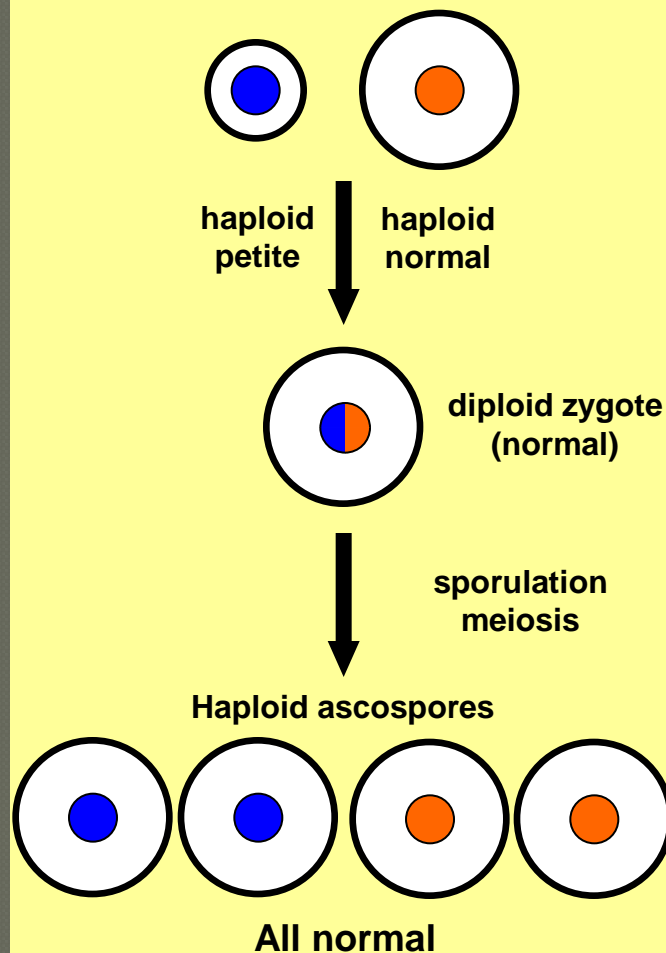
Compare to Fig. 8.4.

*Saccharomyces cerevisiae* (yeast) and the petite mutation:

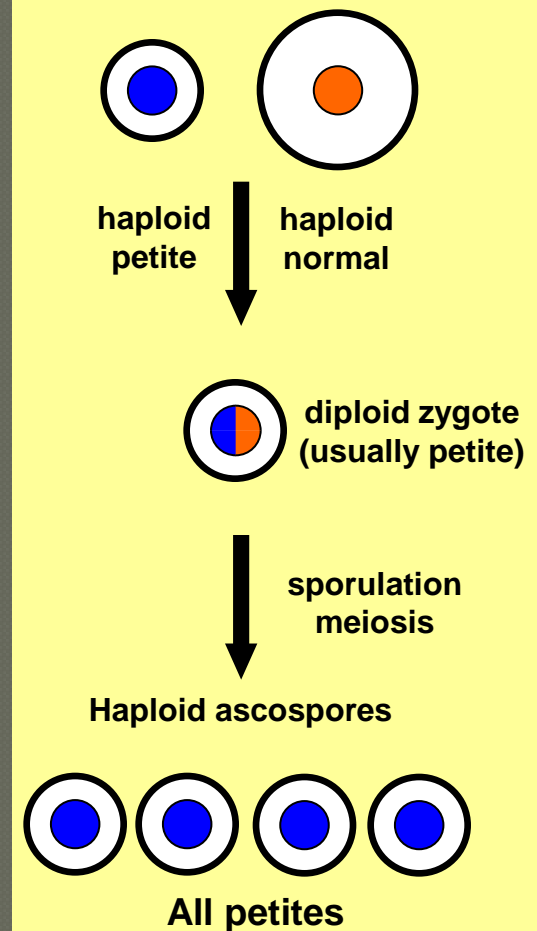
## Segregational



## Neutral



## Suppressive



# Infectious Heredity

A parasite living in the cytoplasm is passed on to the offspring through the mother (**maternal inheritance**).

♀ sensitive x ♂ normal  
↓  
All sensitive

♂ sensitive x ♀ normal  
↓  
All normal

Cause = **Sigma** (A virus found in the cytoplasm.)

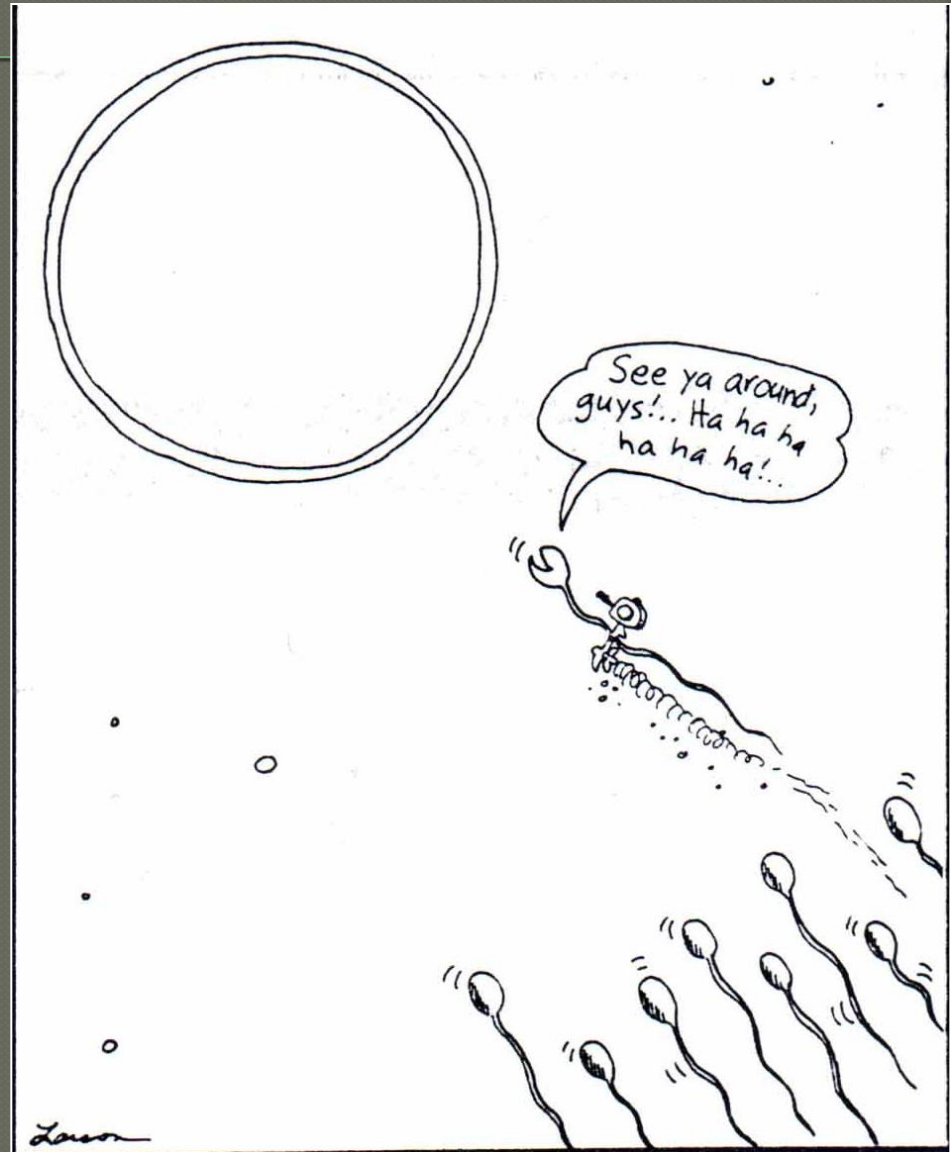
**Q: Why are infertile haplotypes not eliminated by natural selection??**

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- **A: Because human mitochondria are maternally inherited, reductions in male fertility do not reduce their own transmission (fitness). This creates genetic conflict between mitochondrial and nuclear genomes.**

# Why is only male fertility affected??

Sperm are motile and need lots of energy from mitochondria -- mutations causing even slight reductions in OXPHOS efficiency may hurt sperm motility



# Mitochondria also cause male sterility in many plants

*Silene acaulis*

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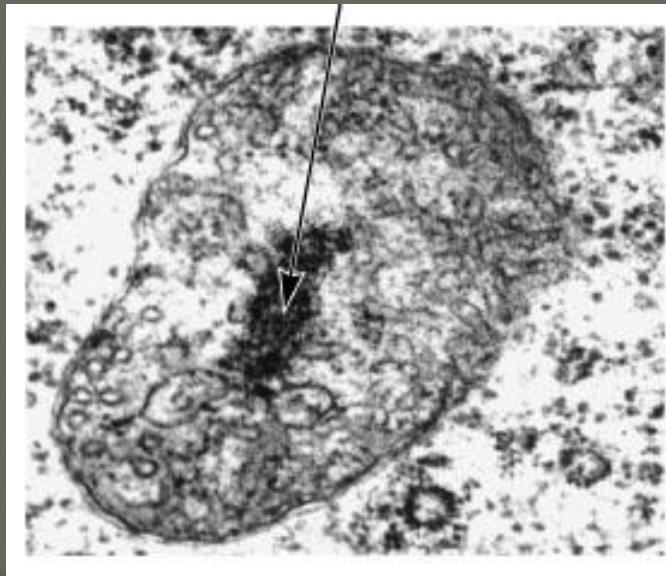
Male sterile (female)



hermaphrodite

# Chloroplasts

- Location of photosynthesis in plant cells
- Haploid (one copy in each individual)
- Maternally inherited in some groups and paternally inherited in others (pine trees)



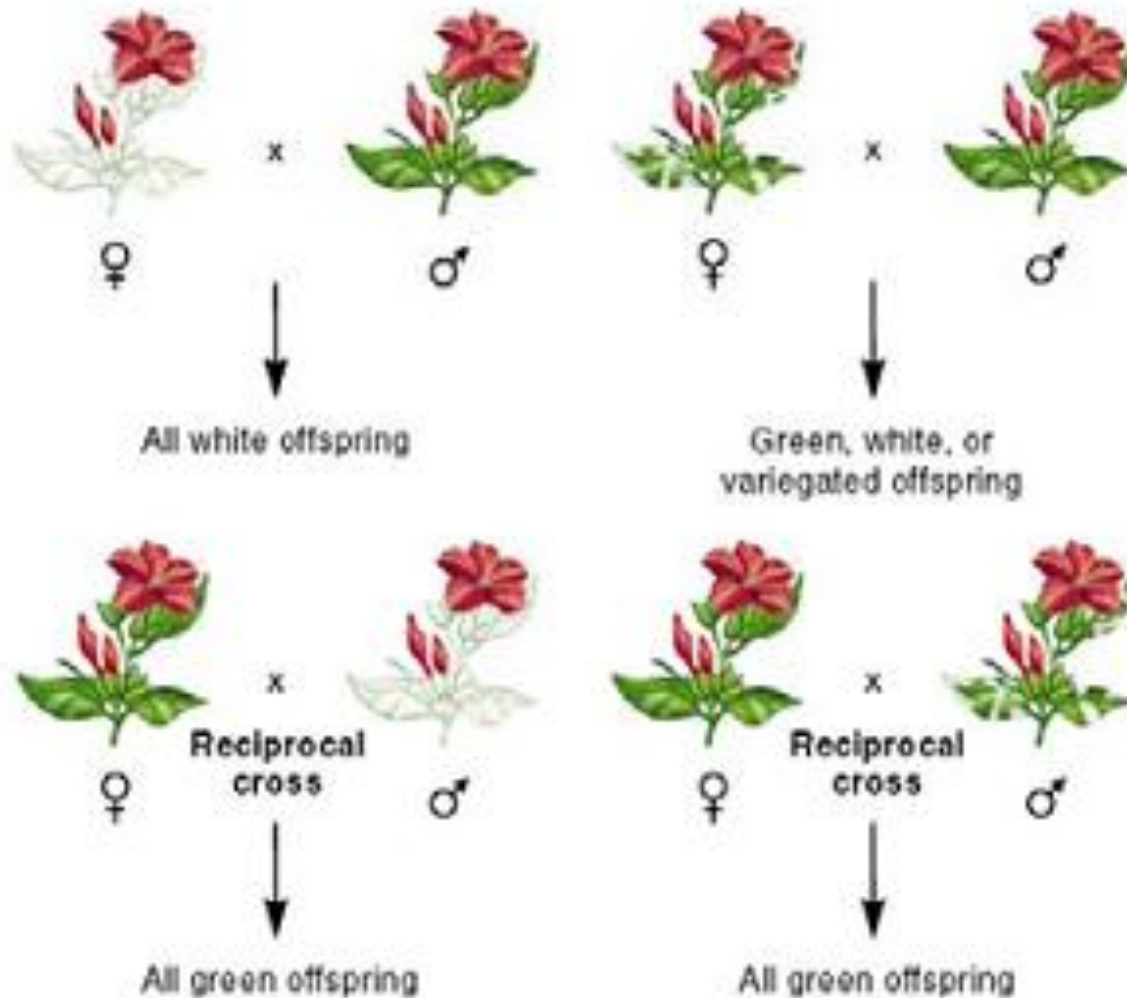
- 
- The main function of chloroplasts is photosynthesis
  - ☐
  - The genetic material in chloroplasts is referred to as cpDNA
  - It is typically about 10 times larger than the mitochondrial genome of animal cells
  - ☐
  - The cpDNA of tobacco plant consists of 156,000 bp
  - It carries between 110 and 120 different genes rRNA and tRNA genes
  - ☐
  - Many genes that are required for photosynthesis
  - As with mitochondria, many chloroplast proteins are encoded by genes in the nucleus
  - ☐
  - These proteins contain chloroplast-targeting signals that direct them from the cytoplasm into the chloroplast

# Maternal inheritance on *Mirabilis jalapa*

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- [Carl Correns discovered that pigmentation in *Mirabilis jalapa* (the four o'clock plant) shows a non-Mendelian pattern of inheritance
- [Leaves could be green, white or variegated (with both green and white sectors)
- Maternal Inheritance in the Four-o'clock Plant
- [Correns determined that the pigmentation of the offspring depended solely on the maternal parent and not at all on the paternal parent
- [This is termed maternal inheritance

# Maternal inheritance on *Mirabilis jalapa*



# Four O'Clocks

<i>Source of Pollen</i>	<i>Location of Ovule</i>		
	White branch	Green branch	Variegated branch
<b>White branch</b>	White	Green	White, green, or variegated
<b>Green branch</b>	White	Green	White, green, or variegated
<b>Variegated branch</b>	White	Green	White, green, or variegated



- 
- In this example, maternal inheritance occurs because the chloroplasts are transmitted only through the cytoplasm of the egg
  - The pollen grains do not transmit chloroplasts to the offspring
  - The phenotype of leaves can be explained by the types of chloroplasts found in leaf cells
  - **Green phenotype is the wild-type**
  - **Due to normal chloroplasts that can make green pigment**
  - White phenotype is the mutant
  - **Due to a mutation that prevents the synthesis of the green pigment**
  - **A cell can contain both types of chloroplasts**
  - **A condition termed heteroplasmy**
  - **In this case, the leaf would be green**

# Human Disease

- Human mtDNA is transmitted from mother to offspring via the cytoplasm of the egg
- Therefore, the transmission of human mitochondrial diseases follows a strict maternal inheritance pattern
- Several human mitochondrial diseases have been discovered
- These are typically chronic degenerative disorders affecting the brain, heart, muscles, kidneys and endocrine glands
- Example: Leber's hereditary optic neuropathy (LHON)
- Affects the optic nerve
- May lead to progressive loss of vision in one or both eyes
- LHON is caused by mutations in several different mitochondrial genes

# Genomic imprinting

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- **Genomic imprinting** is a phenomenon in which expression of a gene depends on whether it is **inherited from the male or the female parent**
- Imprinted genes follow a **non**-Mendelian pattern of inheritance
- Depending on how the genes are “marked”, the offspring expresses either the maternally-inherited or the paternally inherited allele
- Not both
- This is termed **MONO ALLELIC EXPRESSION**

# Genomic Imprinting

Whether a gene is active or not depends on if it came from the mother or the father.

## Igf2 in mice

Gene from Dad = **ON**  
Gene from Mom = **OFF**  
(**maternally imprinted**)

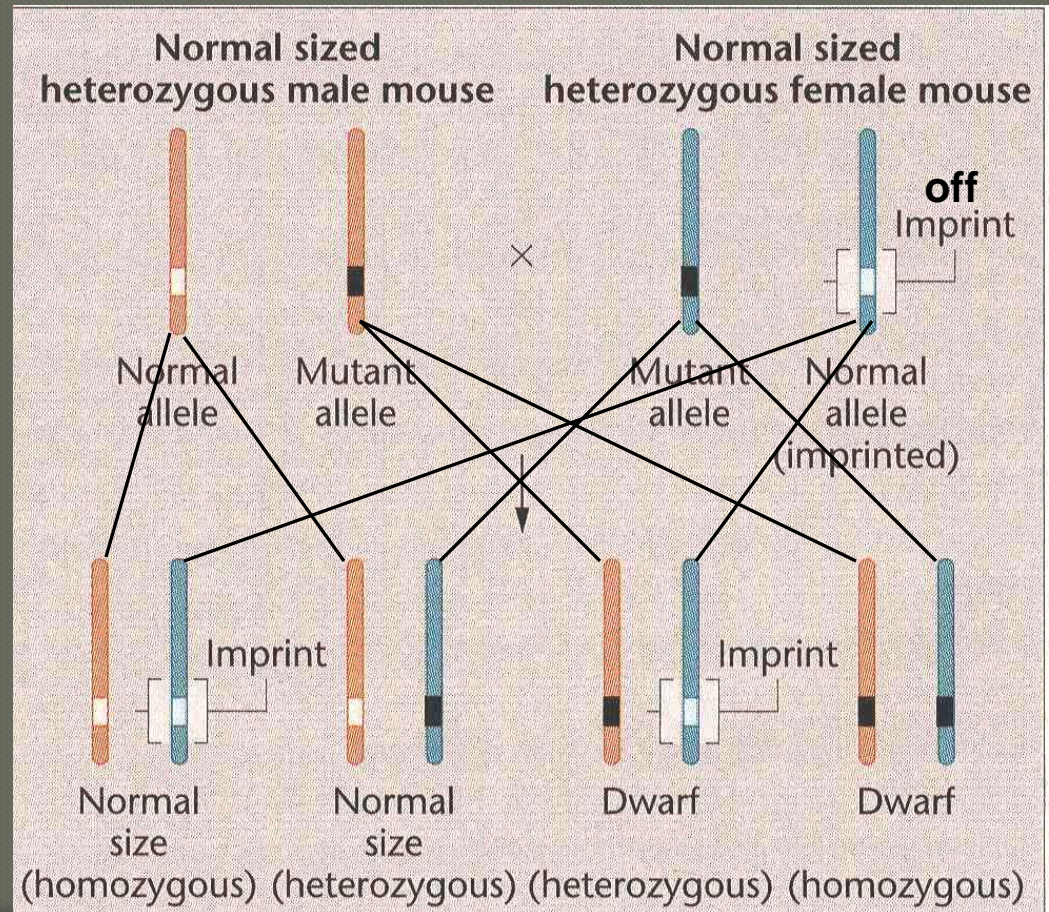
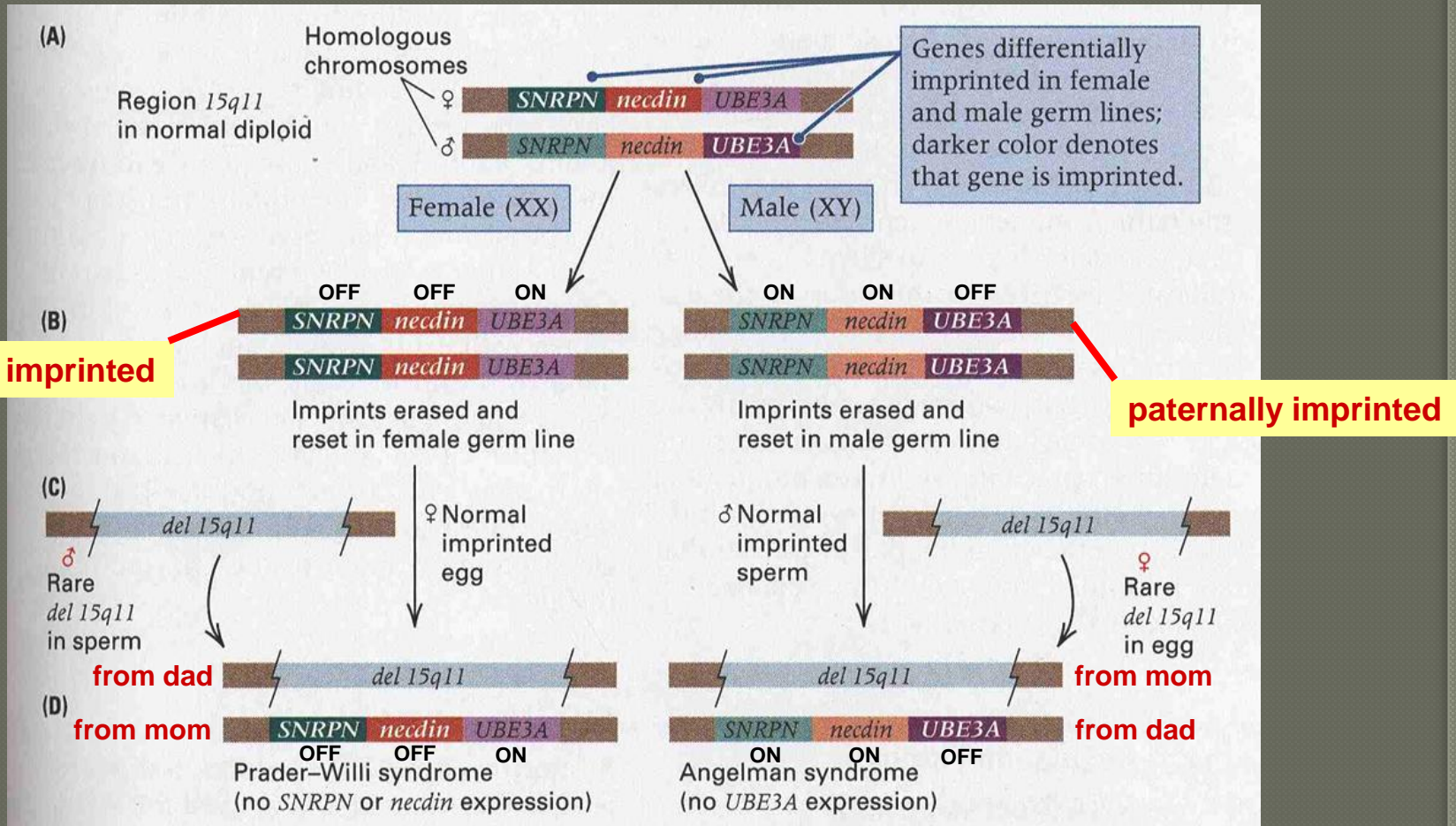


Fig. 4.20

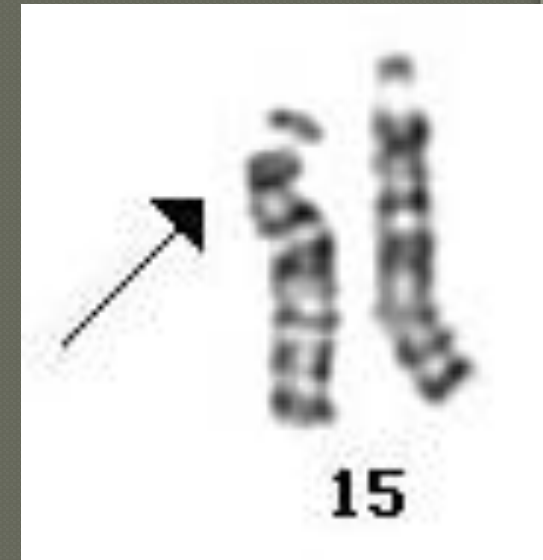
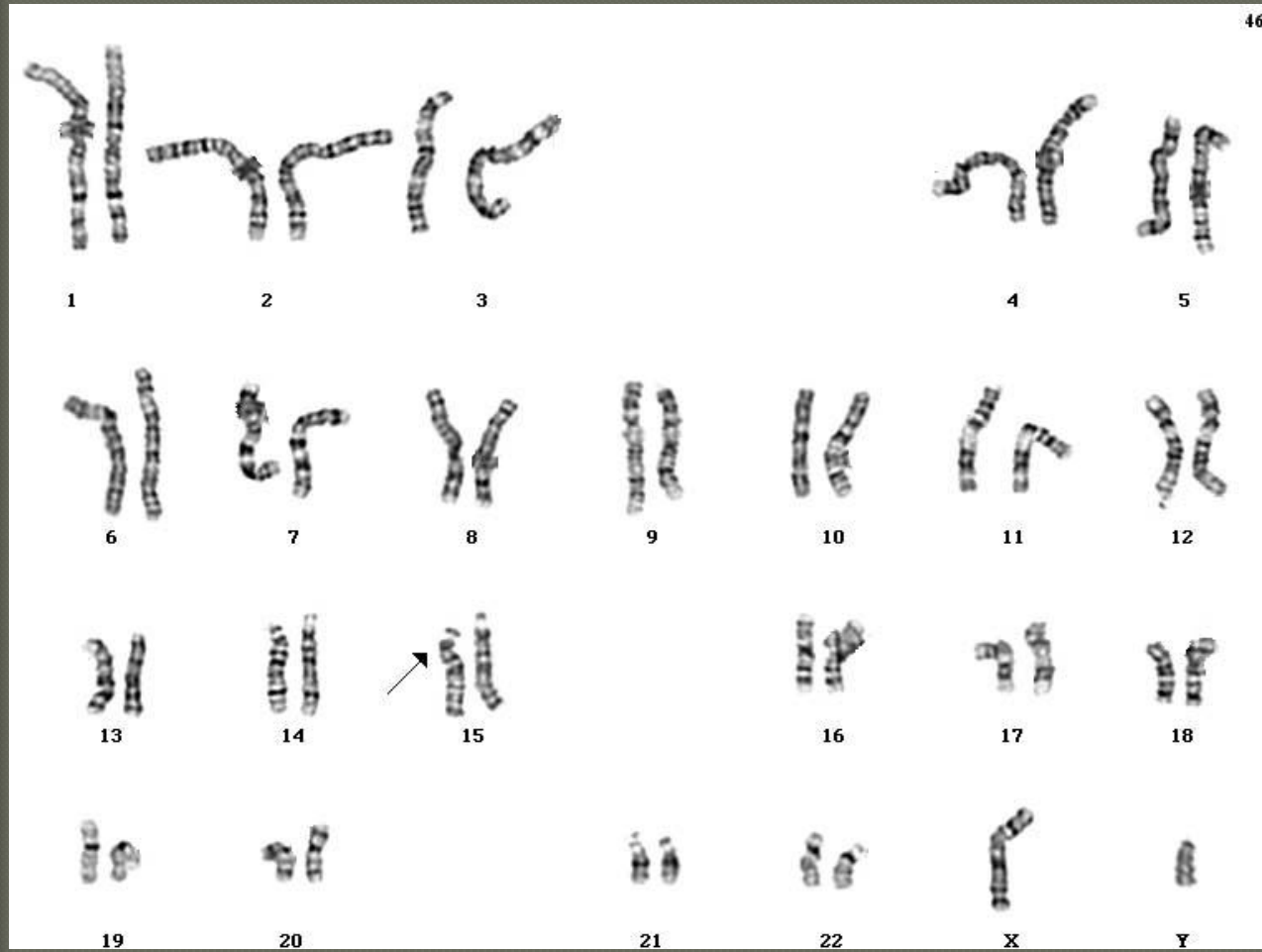
# Example of **genomic imprinting** in humans

## Partial deletion of chromosome 15 (15q11:q13).



**Mechanism:** Increase methylation = Turns genes OFF  
Decrease methylation = Turns genes ON

# Prader-Willi / Angelman Syndrome



## Prader-Willi Syndrome



## Angelman Syndrome



# Dosage Compensation (X-inactivation)

**Humans: XX = female  
XY = male**

**Random inactivation of one of the X chromosomes  
in females during development.**

**Mice: XX = female  
XY = male**

**Early in development the “X” from the father is inactivated.  
Later, during embryonic development, the “X” from the father  
is reactivated and then either the “X” from the mother or father  
is randomly inactivated.**

- Tuliskan urutan DNA sense dan antisense dari mRNA berikut:
- 5'-UAACGCUUGUGCAACCGGUCGGCAAUCC-3'
- Apa perbedaan mol mRNA, tRNA, dan rRNA
- Apa nucleosome itu?
- Mengapa kelainan maternal inheritance lebih berbahaya dibanding dgn chromosomal inheritance