

Modified Mendelian Inheritance

Non –Mendelian/Extra-chromosomal Inheritance

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- The inheritance of the genes located on the chromosomes in the nucleus (i.e. nuclear genes) is referred to as **Mendelian pattern of inheritance**.
- Most of the genes in eukaryotic species follow a Mendelian pattern of transmission.
- Some genes do not follow the classical Mendelian pattern of inheritance (**Non-Mendelian inheritance**).

Criteria for determining Non-mendelian Inheritance

- **Differences in results of Reciprocal crosses:**
- **Lack of Mendelian segregation (Non – Mendelian ratios):** when traits fail to demonstrate classical segregation patterns and deviate from standard ratios, cytoplasmic inheritance is suggested
- **Failure to Show Linkage:** chromosomal genes occupy particular loci. The failure to find linkage of a trait to a trait known to be controlled by nuclear gene may suggest extra-nuclear inheritance.

Three types of non-Mendelian inheritance are recognized:

- Maternal effects
- Extranuclear/ Cytoplasmic Inheritance; Organelle based heredity or genetic systems
- Epigenetic inheritance

Maternal effects

Both the male and female parent genetically contribute equally to the zygote in terms of the chromosomal genes (with the exception of sex chromosomes).

However, the female parent in most species also contributes whole of its cytoplasm. Products of some specific nuclear genes synthesized during oogenesis, are also stored in the cytoplasm.

Maternal effects are the influences of a mother's genotype on the phenotype of her offspring.

Maternal effects are effects of products of mother's genes through her cytoplasm on the phenotype of her offspring.

However, such effects are transient to the offspring and are not transmitted to the next generation.

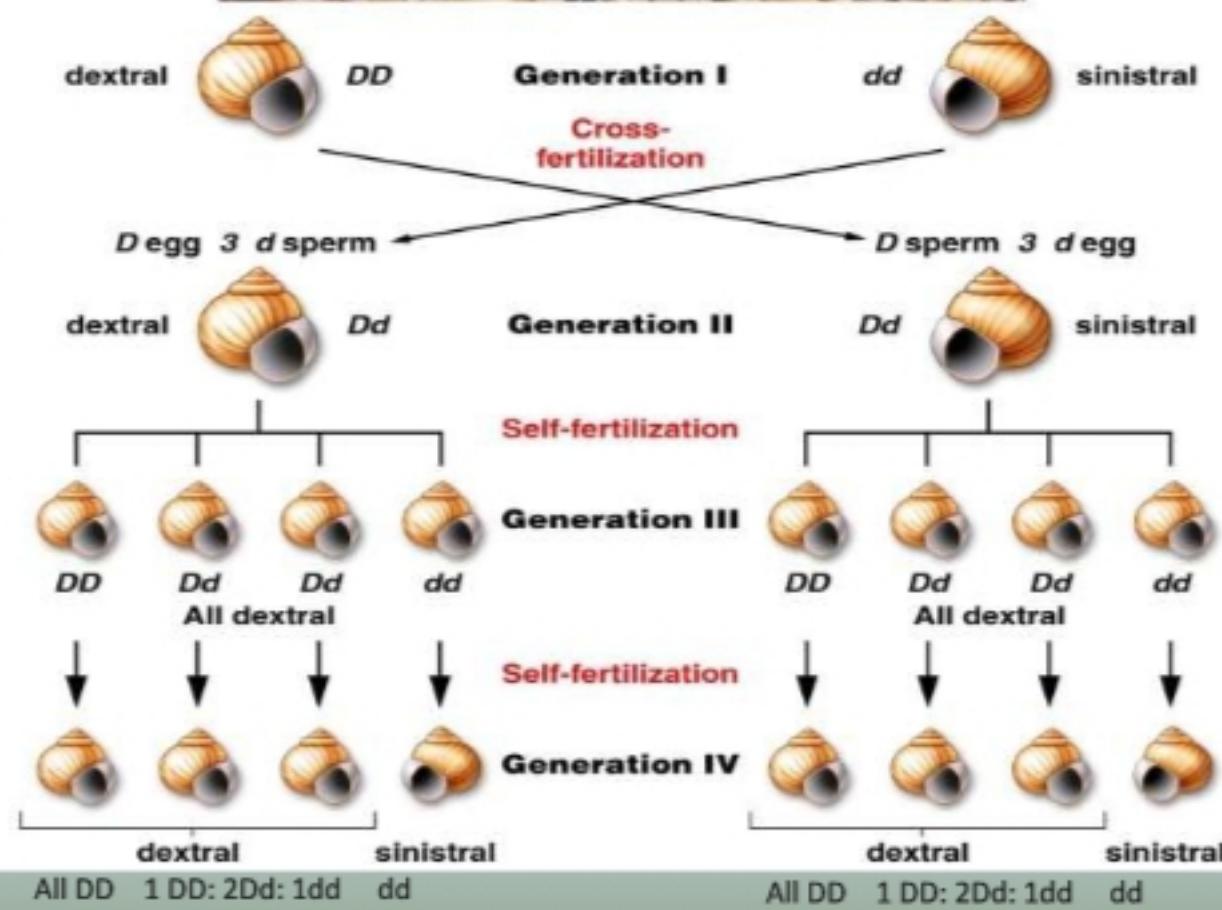
The best example is Snail Coiling:

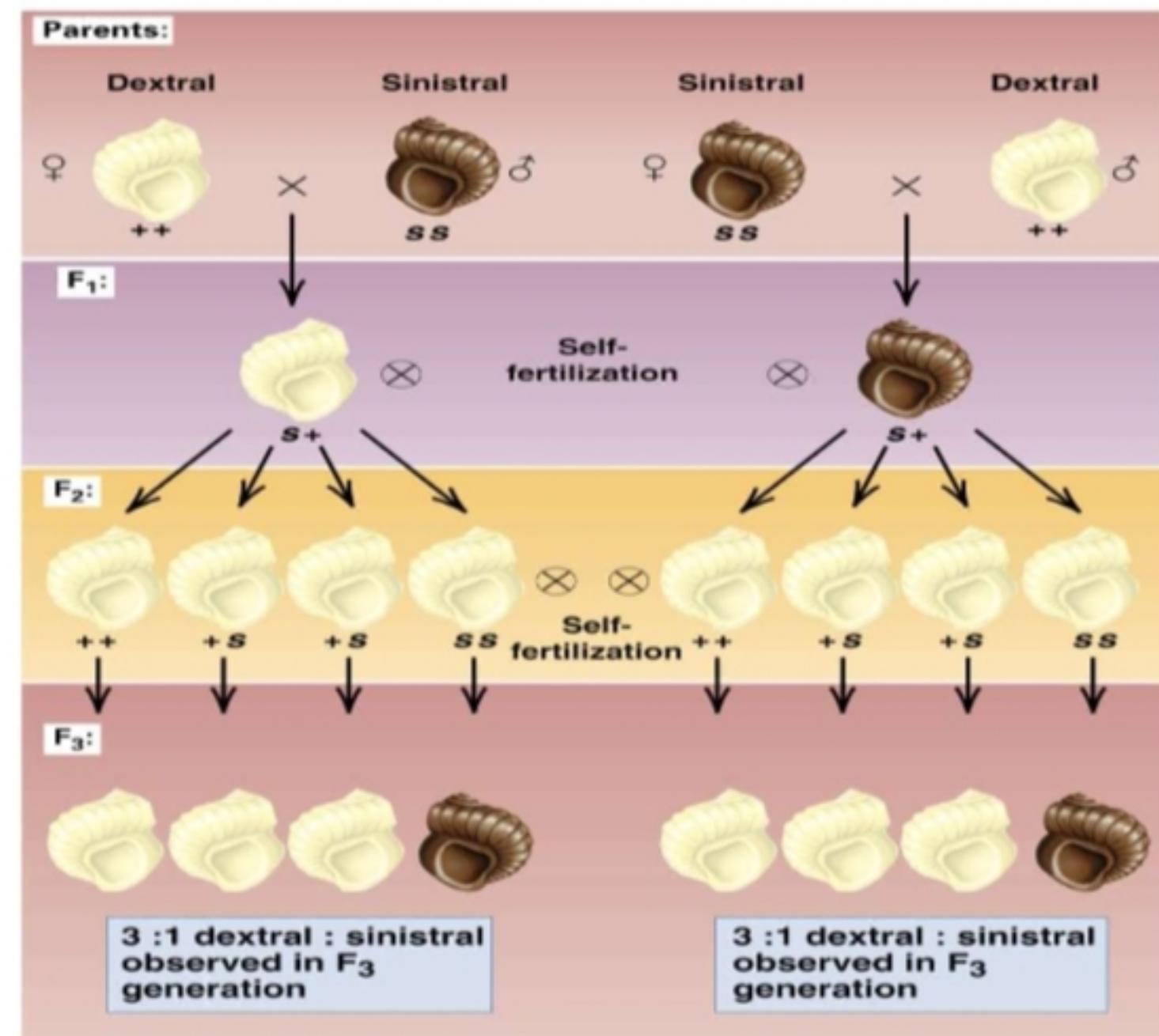
The direction of the coiling of the shell in Limnaea (pond snail) snails illustrates the influence of nuclear genes acting through effects produced in the cytoplasm.

The shells of snails coil either to the right (**Dextral**) or to the left (**Sinistral**).

Direction of coiling is determined by a pair of nuclear alleles:

Dextral D (right) is dominant to Sinistral (d)
but the expression of the phenotype depends on the maternal genotype.





- F1 offspring in both crosses have the same genotype (Dd) but reflect (the phenotype dictated by) the mother's genotype for coiling
- F2 offspring in both the crosses are identical because the genotypes of the F1 mothers are identical (Dd).
- Self fertilization among F2 individuals would result in the F3 generation
- The coiling pattern of the offspring snail is determined by the genotype of the parent producing the egg regardless of the phenotype of that parent.
- Therefore, maternal parents that are DD, Dd produce only dextral coiling.
- Maternal parents that are 'dd' produce only sinistral coiled progeny.

Blockage of Riboflavin transfer to egg

'Rd' allele causes the transfer of dietary riboflavin to egg yolk;

'rd' allele in homozygous state ($rd\ rd$) does not allow the transfer of riboflavin to the egg yolk.

Therefore, the eggs produced by such hens are so deficient in this vitamin such that none of their eggs can sustain an embryo during incubation.

Thus the fate of the developing embryo, irrespective of its own genotype, depends on the genotype of the mother as the product of mother's genotype is stored in egg yolk for utilization by the developing embryo.

The maternal effect are mediated through

- Substances present in the egg: products of some specific nuclear genes synthesized during oogenesis stored in cytoplasm and effect early development
- Development and nurturing effect of mother: intra uterine environment of female mammals and their milk producing ability influence growth and viability of fetus.

In poultry, maternal effects are mediated through egg which provides nourishment to developing embryo.

Extranuclear/Cytoplasmic Inheritance

Two cytoplasmic organelles that contain their own genetic material;
mitochondria and plastids (e.g. chloroplast in plants).

Inheritance associated with their genetic material is called Extra Nuclear inheritance or Cytoplasmic inheritance.

Some organisms also contain intracellular parasites or symbionts including cytoplasmic bacteria, viruses etc. they have their own genetic material.

Extra nuclear or cytoplasmic inheritance is defined as inheritance of cytoplasmic organelles (mitochondria and plastids) and parasites or symbioants that have their own genetic material.

Extra nuclear inheritance has two components:

- Organelle Heredity and
- Infectious Heredity

Molecular genetics and discovery of DNA in mitochondria (animals) and chloroplast (plants) has recognized Extra nuclear inheritance as an important aspect of genetics and special branch called “Development Genetics”

Organelle Heredity- Mitochondria (animals) and Chloroplast (plants)

Mitochondria are small cytoplasmic self replicating organelles specialized for respiration.

Mitochondrial DNA which is circular in form contains a relatively small number of genes.

Mitochondria are generally inherited in maternal fashion i.e. male gamete do not contribute mitochondria to zygote.

In Humans, a point mutation in mitochondrial causes **Leber's optic atrophy (cytoplasmically inherited)** i.e. bilateral blindness with average age of onset of 20 -24 yrs.

This is because defects in mitochondria are not tolerable in the optic nerve which has a very great energy demand.

It was determined from pedigrees that the disease was transmitted only maternally.

DNA sequencing in affected families resulted in identifying the disease to a point mutation.

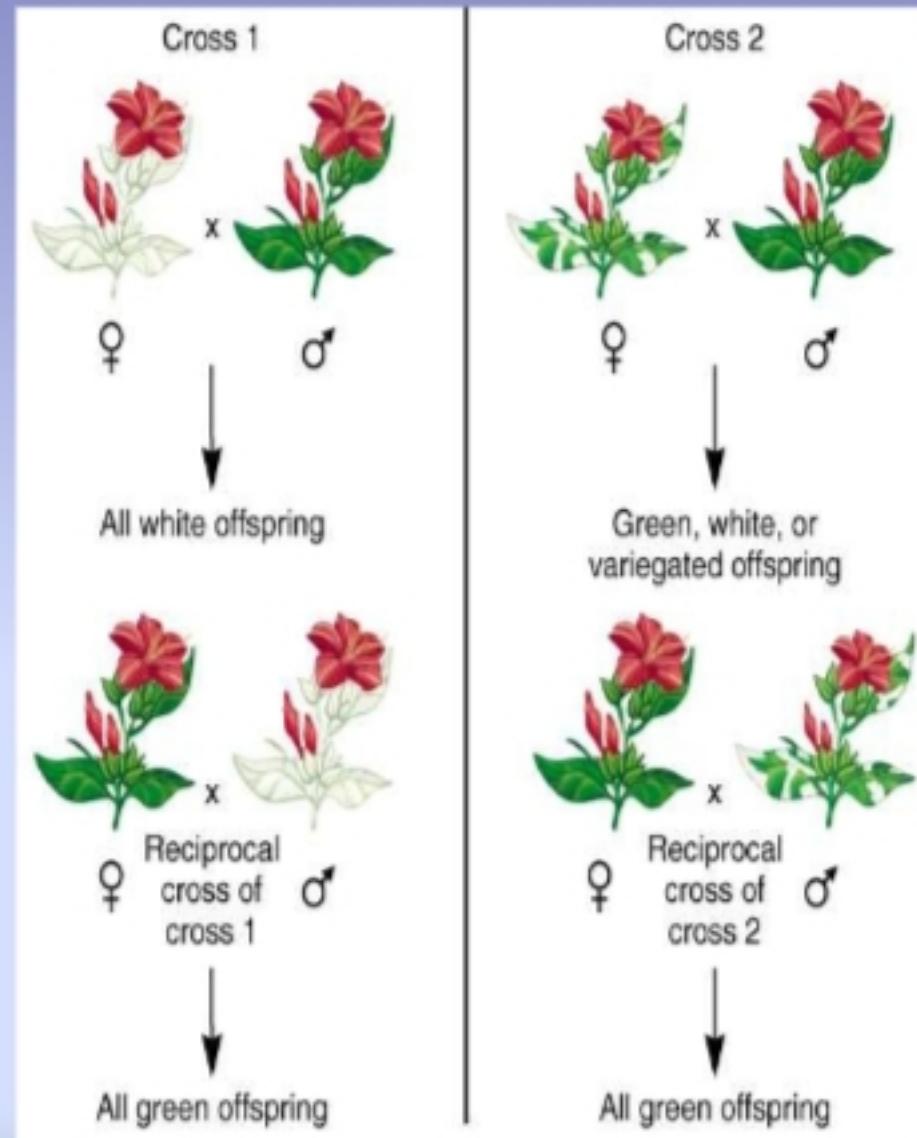
This is the first disease traced to a specific mitochondrial DNA mutation.

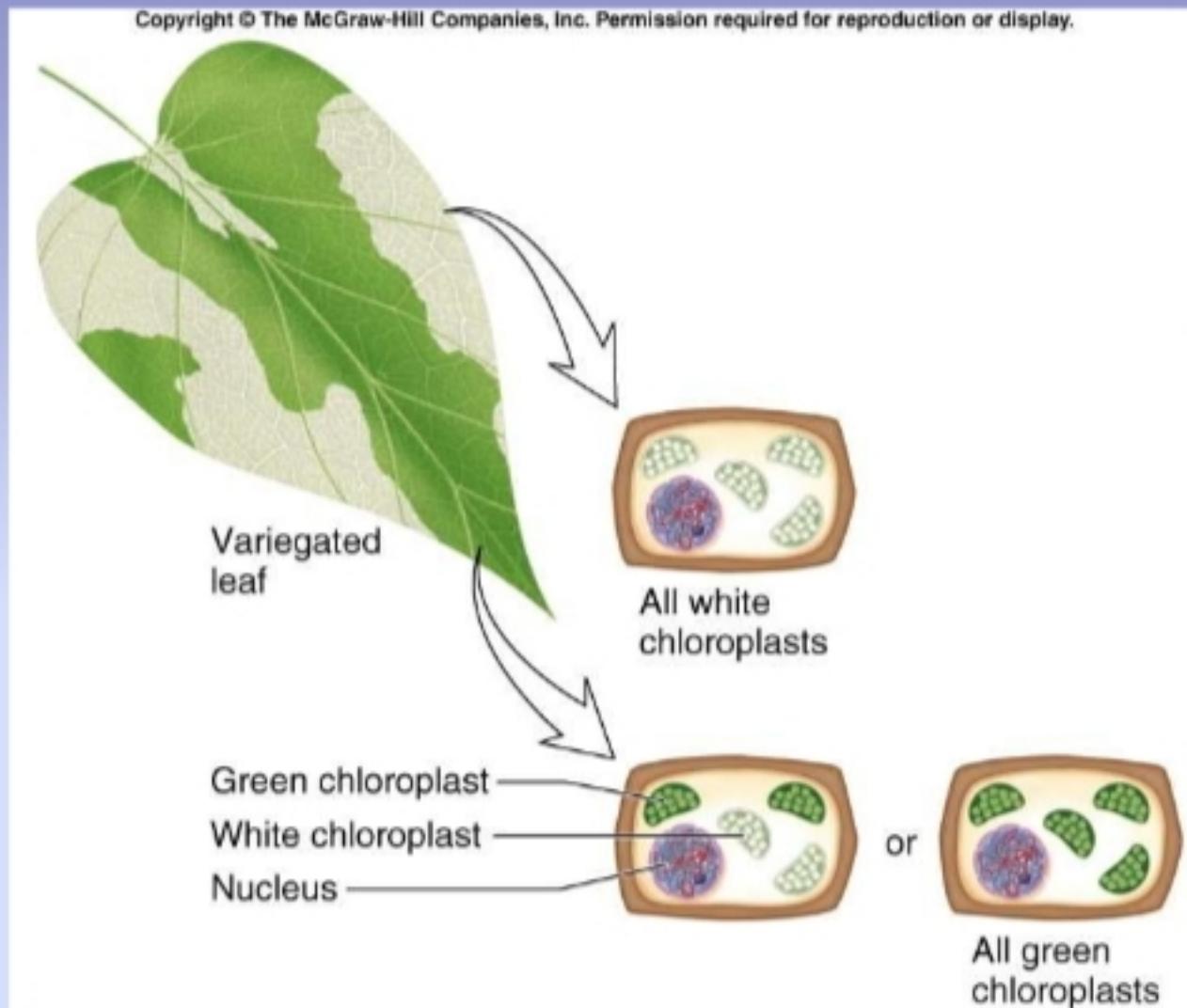
Chloroplast is a chlorophyll containing organelle that carries out photosynthesis and starch grain formation in plants.

Like mitochondria, chloroplasts contain DNA and ribosomes. DNA of chloroplasts is circular.

Variegation in four o' clock plant is example of inheritance related to chloroplasts.

- Pigmentation in *Mirabilis jalapa* offspring depends solely on the maternal parent
 - “Maternal inheritance”
 - Chloroplasts are inherited only through the cytoplasm of the egg





Infectious Heredity

- In eucaryotes, presence of bacteria and viruses which live in their cytoplasm may influence some traits.
- They coexist in a symbiotic relationship and passed through maternal cytoplasm to progeny
- Some individuals of the protozoan *Paramecia aurelia* possess the “killer” trait i.e. Secrete the toxin *paramecin* which kills many strains of paramecia

Epigenetic Inheritance

Epigenetic inheritance is a pattern in which a nuclear gene/chromosome is altered but the change in gene expression is not permanent over generations.

Features of epigenetic inheritance are:

1. Epigenetic changes are caused by DNA and chromosomal modifications during gametogenesis and/or early embryogenesis.
2. Once they occur, epigenetic changes alter the expression of a particular gene in a way that may be fixed during an individual's life time.
3. Epigenetic modifications are not permanent over generations

Two examples of epigenetic inheritance are

- Dosage compensation
- Genomic imprinting

Dosage Compensation of X-Linked Genes

- Males and females of many species have different numbers of sex chromosomes
 - XX chromosomes in female and XY in male
 - The level of expression of many genes on sex chromosomes is similar in both sexes

Dosage compensation is the mechanism that equalizes the level of expression of genes on the X chromosome in the two sexes even though males and females have different number of X chromosomes.

In other words, Dosage compensation ensures that one sex does not have differential activity of alleles on the sex chromosomes.

The term dosage compensation was coined by **Muller** (1931) at the University of Texas (USA) to explain the effects of sex –linked eye colour genes in Drosophila.

Two mechanism may be account for dosage compensation:

- One copy of each X-linked gene could be inactivated in females (**Inactivation**),
- Each X-linked gene could work twice as much in males as it does in females (**Hyper Activation**).

Extensive research has shown that both mechanisms are utilized, the first in mammals and the second in Drosophila.

Inactivation of X-linked Genes in Female Mammals

Dosage compensation of X-linked genes is accomplished by **inactivation of one of the female's two X- chromosomes**.

Both the females and males have only one functional X chromosome per cell .

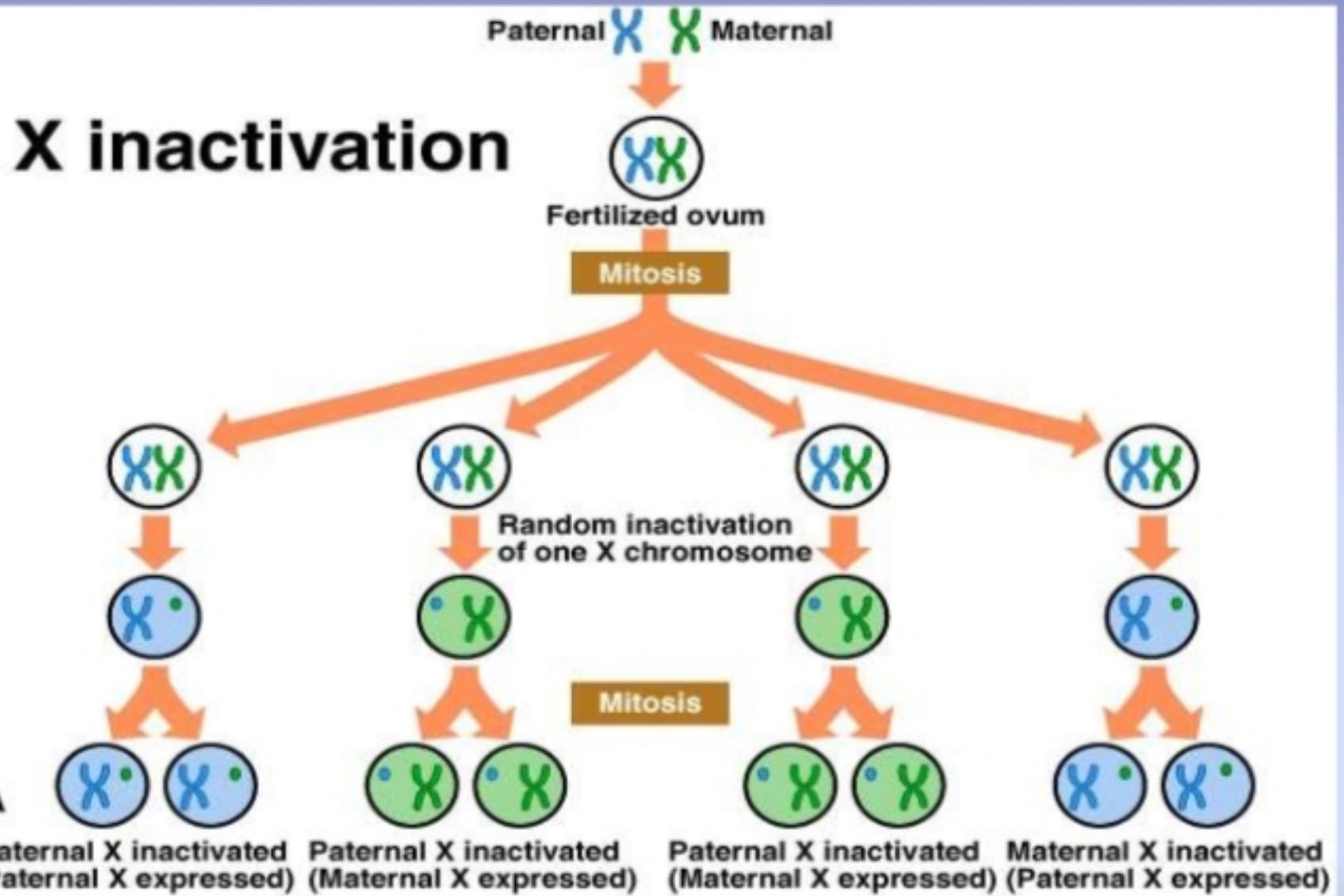
This mechanism of inactivation of one X-linked genes was first proposed by the British geneticist, Marry **Lyon** (1961) who inferred it from studies on mice (hence, it is also referred to as **Lyon's hypothesis**).

Features of X inactivation are

1. The X-chromosome inactivation occurs very early in embryonic development
2. One X-chromosome in each somatic cell is genetically inactivated.
3. The chromosome to be inactivated is chosen at random,
4. Once the choice is made, the same X-chromosome remains inactive in all of the descendants of that cell.

Normal female mammals are '**Genetic Mosaics**' (for X-linked genes) containing two types of cell lines.

The maternally inherited X-chromosome is inactivated in roughly half of these cells, and the paternally inherited X is inactivated in the other half.



Phenotypic evidence for X-chromosome inactivation the Calico cat

Coat colour in cats is governed by an X-linked gene; one allele results in orange coat and the other allele causes black coat.

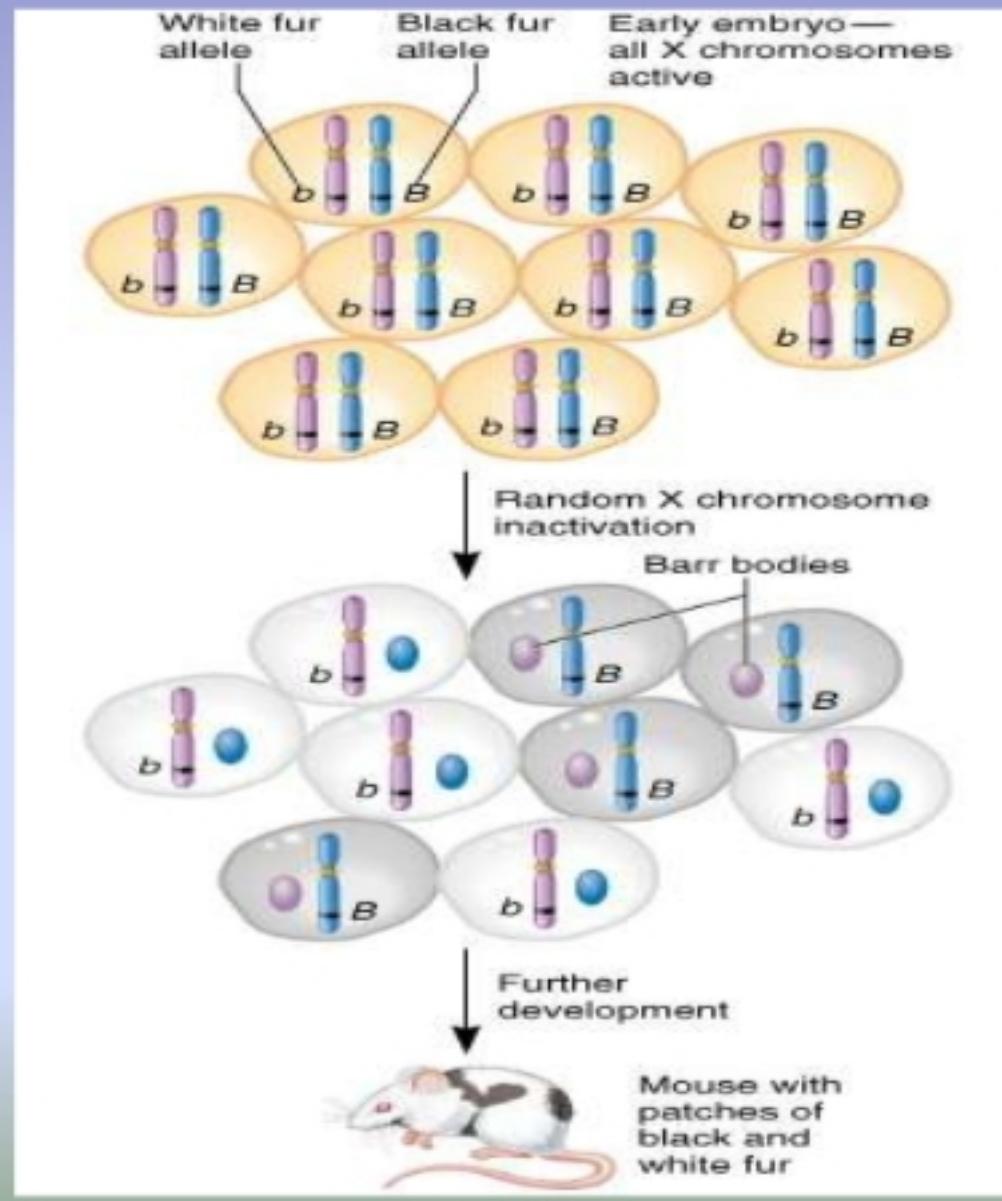
Normal male has only one X-chromosome, therefore, he has either orange or black coat.

Female cat can, however, be heterozygous for 'orange' and 'black' alleles. A heterozygous female shows patches of orange-fur, corresponding to one allele, and black-fur, corresponding to other allele, with white patches on lower side of body (**Calico Pattern**)

The orange and black patches result from X chromosome inactivation in different cell lines.



Similar type of coat colouration has also been identified in the mouse



X-chromosome inactivation

- Levels of enzymes or proteins encoded by genes on the X chromosome are the same in both males and females
- e.g. G6PD, glucose 6 phosphate dehydrogenase, gene is carried on the X chromosome which codes for an enzyme that breaks down sugar
- Females produce the same amount of G6PD enzyme as males

X-chromosome inactivation

- XXY and XXX individuals produce the same amount of G6PD as anyone else
- In cells with more than two X chromosomes, only one X remains genetically active and all the others become inactivated.
- In XXX and XXXX females and XXY males only 1 X is activated in any given cell the rest are inactivated

Cytological Evidence

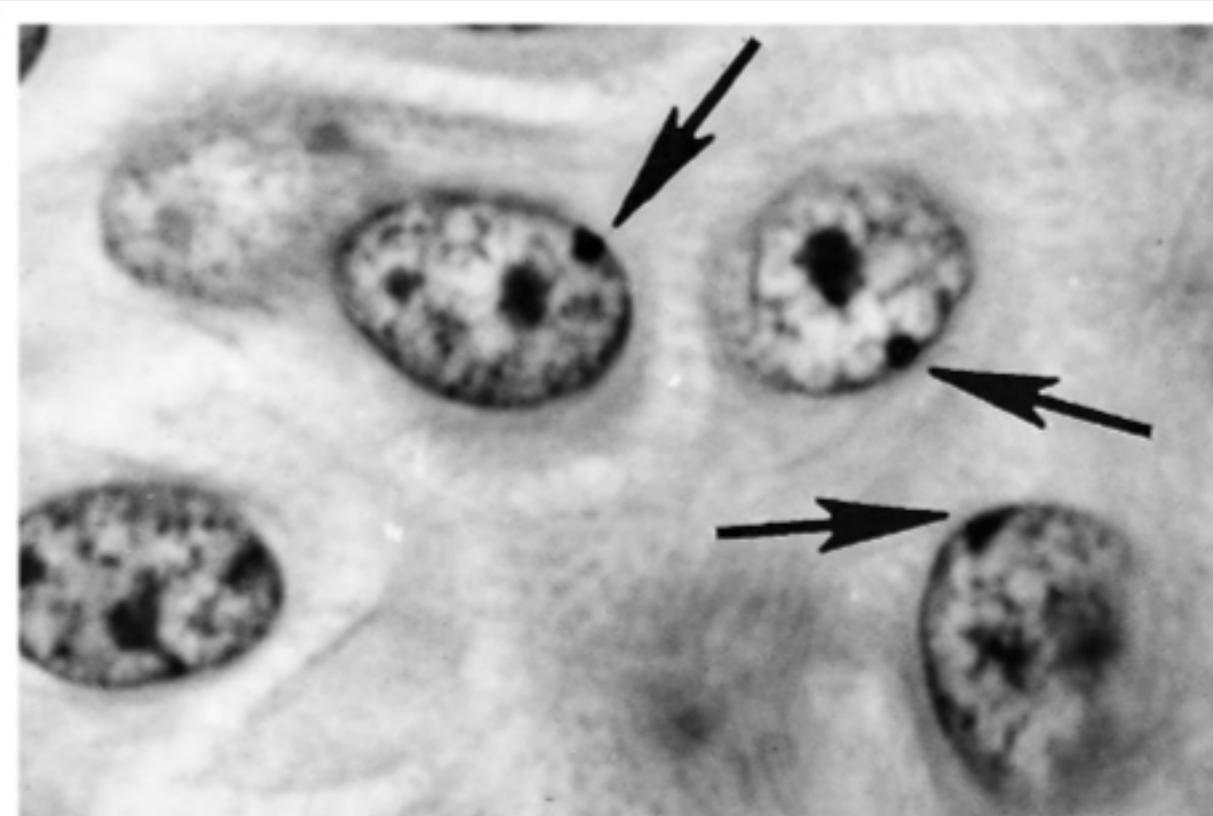
The inactive X-chromosomes in females is seen in the nucleus of interphase cells as a condensed, darkly-staining (heterochromatic) body, attached to the inner surface of nuclear membrane called the **Barr body**.

Barr and Bartman, the Canadian scientists in 1949 noted that normal female cats show a single condensed body whereas males show none, referred to the body as '**Sex-chromatin**' which has since been referred to as **Barr body** (named after Murray Barr, the first author of the report).

It was, however, **Lyon** (1961 in England) who suggested that *Barr body represented an inactive X chromosome which in females becomes tightly coiled into heterochromatin, a condensed, and ,therefore, visible form of chromatin.*

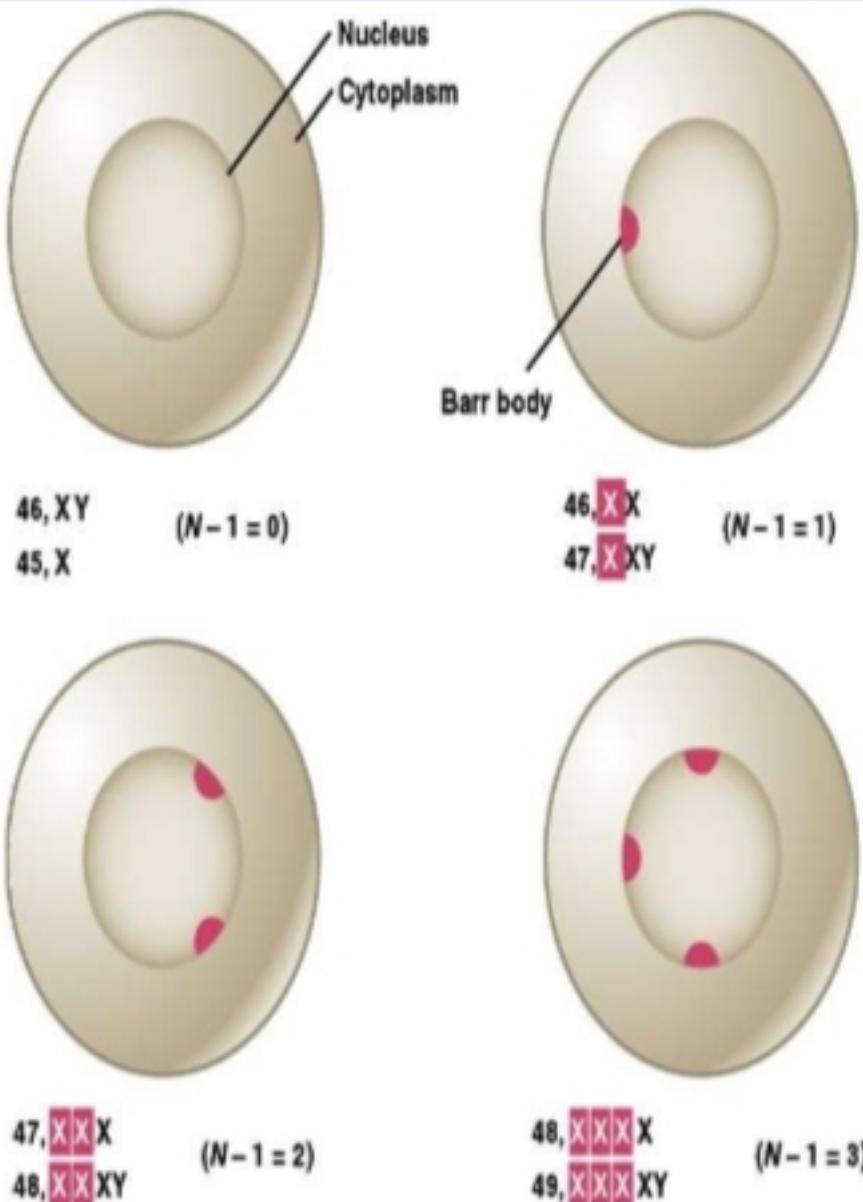
The inactivated X chromosome remains in this altered state in all the somatic tissues.

Barr Bodies



From N. Aron/Delmar, Figure 9.8, Biogear World, 1973

Barr bodies represent the inactive X chromosome and are normally found only in female somatic cells.



■ A woman with the chromosome constitution $47, \text{XXX}$ should have 2 Barr bodies in each cell.

■ XXY individuals are male, but have a Barr body.

■ XO individuals are female but have no Barr bodies.

Hyper activation of X-linked Genes in Male Drosophila

In Drosophila, the dosage compensation of X-linked genes is achieved by an increase in the activity of X-linked genes in males.

Hyperactivation involves a complex of different proteins that binds to many sites on the X chromosome in males, and triggers a doubling of gene activity.

Total X-linked gene activity in males and females is approximately equalized.

Even though dosage compensation is widespread among animal species, but it is not universal as:

- Certain species, such as birds and butterflies, may not compensate for differences in the number of sex chromosomes.

Gene Imprinting

Gene/genetic/genomic/molecular imprinting refers to a phenomenon in which the expression of a gene/allele varies depending upon whether it has come from the father or the mother

A segment of DNA (i.e gene) is marked, and that mark is retained or recognized throughout the life of the organism inheriting the marked gene.

The marking process causes the offspring to distinguish between maternally and paternally inherited alleles depending on how the genes are marked.

e.g. mouse growth hormone gene called insulin-like growth factor II (*Igf-2*)

- The *Igf-2* gene encodes an insulin-like growth factor
 - Functional allele required for normal size
 - *Igf-2m* allele encodes a non-functional protein
- Imprinting results in the expression of the paternal allele only
 - Paternal allele is transcribed
 - Maternal allele remains transcriptionally silent

The imprint of the *Igf-2* gene is erased during gametogenesis

- A new imprint is then imparted
 - Oocytes possess an imprinted gene that is silenced
 - Sperm possess a gene that is not silenced
- The phenotypes of offspring are determined by the paternally derived allele

Igf-2m Igf-2m ♀ x Igf-2 ♂

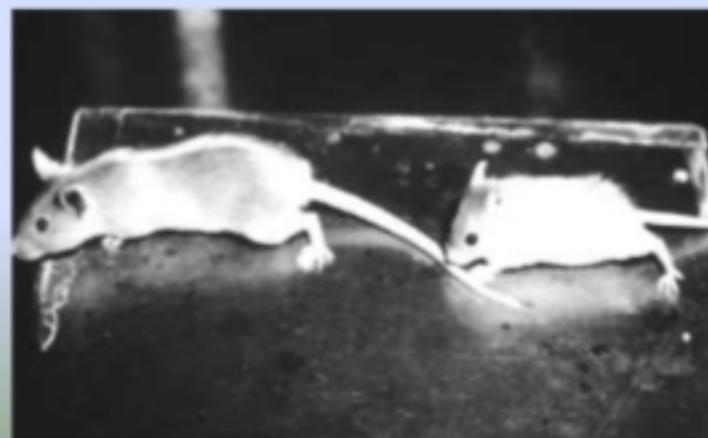
Normal offspring (*Igf-2m Igf-2*)

Igf-2m ♂ x Igf-2 Igf-2 ♀

Dwarf offspring (*Igf-2m Igf-2*)

Different results in reciprocal crosses generally indicate sex-linked traits.

Here it indicates genomic imprinting of autosomal alleles



Imprinting at the cellular level can be divided into three stages:

1. The establishment of the imprint during gametogenesis
2. The maintenance of the imprint during embryogenesis and in adult somatic cells
3. Erasure and reestablishment of the imprint in the germ cells.

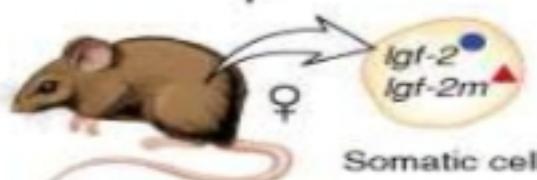
Establishment of the imprint

In this example, imprinting occurs in the *Igf-2* gene, which exists in the *Igf-2* allele from the male and the *Igf-2m* allele from the female. This imprinting occurs so that the paternal allele is expressed.



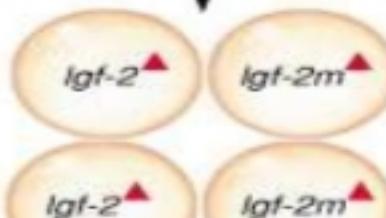
Maintenance of the imprint

After fertilization, the imprint pattern is maintained throughout development. In this example, the maternal *Igf-2m* allele will not be expressed in the somatic cells. Note that the offspring on the left is a female and the one on the right is a male.

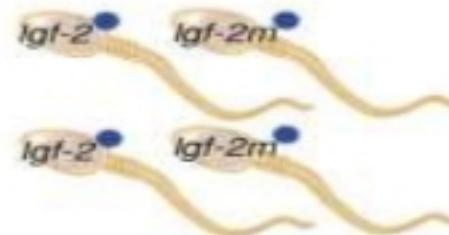


Erasure and reestablishment

During gametogenesis, the imprint is erased. The female mouse produces oocytes in which the gene is silenced. The male produces sperm in which the gene can be transcribed into mRNA.



Oocytes carry
silenced alleles



Sperm carry
expressed alleles

- ▲ Silenced allele
- Transcribed allele

- Occurs in several species
 - Numerous insects, plants, and mammals
- Effects can include
 - A single gene
 - A part of a chromosome
 - An entire chromosome
 - All the chromosomes from one parent

In humans two disorders associated with deletion in chromosome 15 exhibit imprinting:

Prader willi syndrome: effected individual has severe eating disorder marked by uncontrollable appetite, obesity, diabetes and mental retardation

Angelman syndrome: erratic jerky movements with mental retardation

When the undeleted chromosome 15 is maternal- Prader willi syndrome

When the undeleted chromosome 15 is paternal- Angelman syndrome

Thus a region of chromosome 15 is imprinted differentially in male and female gametes and both maternal and paternal regions of chromosome 15 are required for normal development.



THANKS FOR YOUR
ATTENTION