GENETICS

Lect. 4

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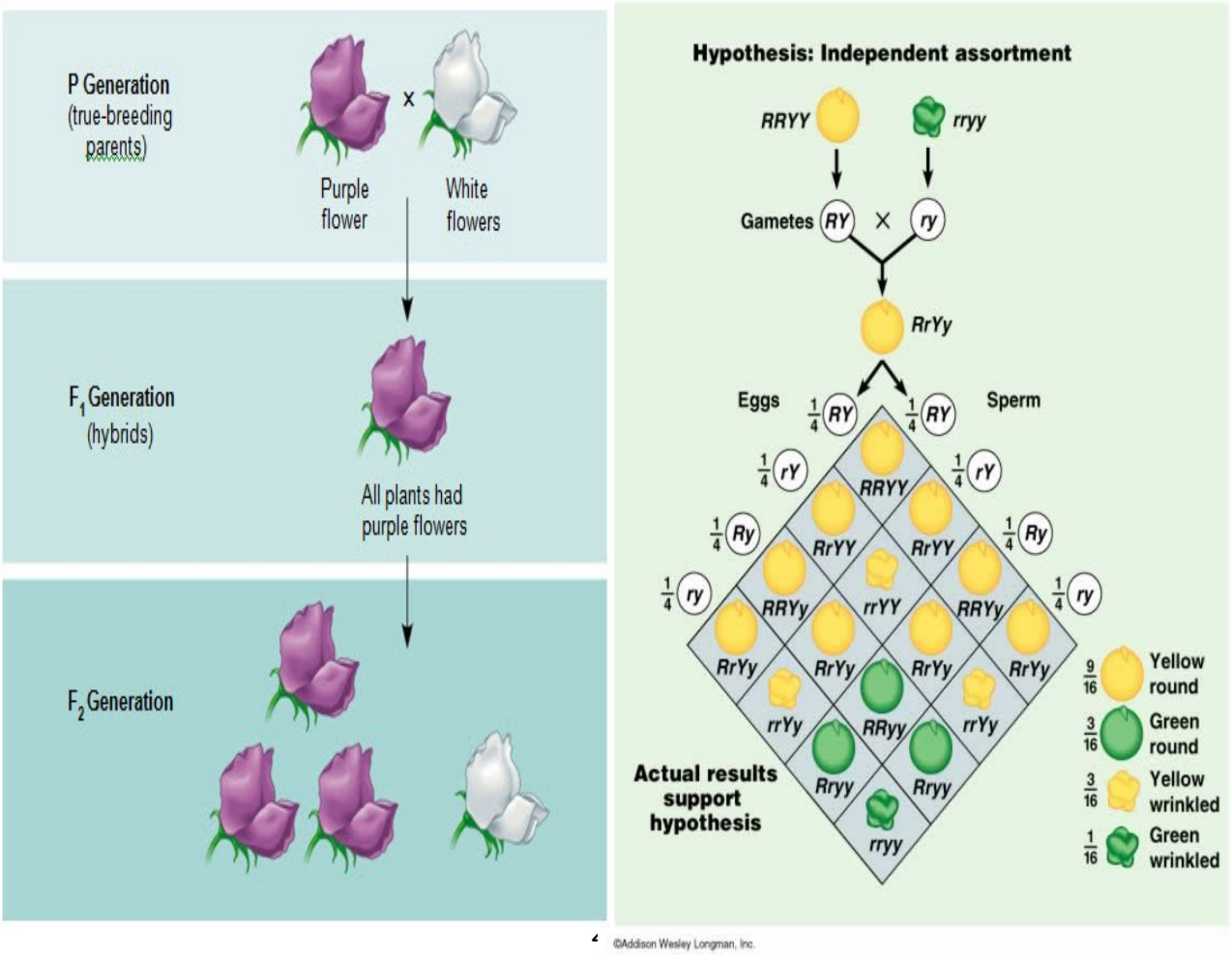
4. EXTENSION OF MENDELIAN INHERITANCE: BEYOND MENDELIAN GENETICS

Mendelian genetics was about: (revise)

Nuclear monogenic genes, each consists of only 2 alleles present on different chromosomes following the rule of complete dominance (simple dominance): **One copy** of the dominant allele is sufficient to produce the dominant phenotype. Recessive allele **does not affect** the phenotype of heterozygotes. The phenotype of the homozygous dominant (AA) organism is similar to that of the heterozygous one (Aa).

The gene obeys both Mendel laws: Monohybrid cross produces 3:1 phenotypic ratio of F_2 and Dihybrid cross produces 9:3:3:1 phenotypic ratio of F_2.



Non-Mendelian inheritance is a general term that refers to any pattern of inheritance in which traits do not segregate in accordance with Mendel's laws and do not express a typical dominance/recessive relationship. That is, the F_1 and F_2 values do not match the predicted values of the proportions of progenys' phenotypes observed by Mendel.

There are several situations in which the proportions of phenotypes observed in the progeny do not match the predicted values.

Exceptions to, or **violations of, Mendel's laws**: What can cause there to be exceptions to Mendel's laws?

1. **non-disjunction**: The segregation of alleles is prevented if homologous chromosome pairs fail to separate during meiosis 1.
2. **gene linkage**: This can prevent independent assortment. Linked genes are on the same chromosome. Genes that are on the same chromosome can be inherited together, but crossing over during meiosis may separate them.
3. **mutation** is a permanent change of the nucleotide sequence of the genome of an organism, virus, or extrachromosomal genetic element. Mutations result from unrepaired damage to DNA or to RNA genomes (typically caused by radiation or chemicalmutagens).

There are several situations in which reject Mendel rules and laws:

I. Monogenic inheritance: allelic relationships
II. Monogenic inheritance: gene action
III. Polygenic inheritance: gene interaction.
IV. Sex related gene: Sex-linked, sex influenced and sex limited
V. Cytoplasmic inheritance
VI. Environmental effects on gene expression

I. For single-gene inheritance: Allelic relationships in genes

Allelic relationships of genes may be:

A. No dominance relations

B. Lethal genes

C. Multiple alleles

A. No dominance relations in Eukaryotic organisms

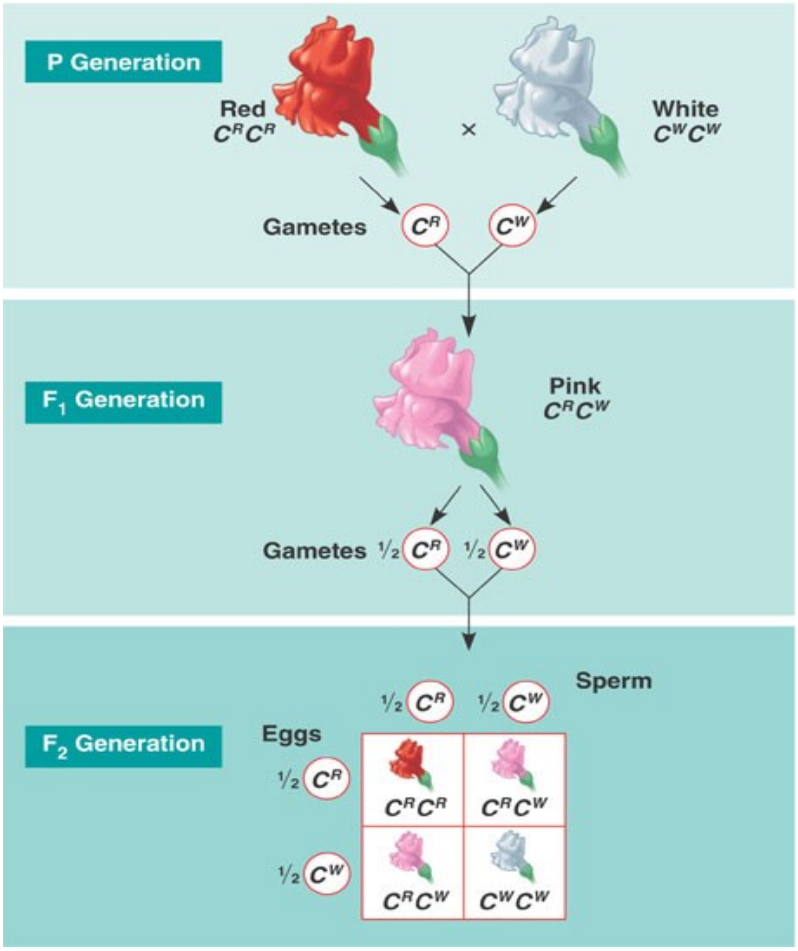
Mendel's followers have revealed the appearance of phenotypes in new ratios that **do not express** a typical dominance/recessive (complete dominance) and **do not obey** Mendel's first law. That is, the F_1 and F_2 do not match the predicted values of the proportions of progenies' phenotypes observed by Mendel. Those different phenotypic dominances were incomplete, partial, co- and over-dominance and can be explained as followings:

1. Incomplete (Intermediate) Dominance

A dominant phenotype is not expressed even though an individual carries a dominant allele i.e. **not fully dominant**. So, the phenotype of the heterozygous organism (Aa) is in **intermediate state** between the phenotype of both homozygous dominant and recessive (AA and aa) organisms i.e. AA phenotype ≠ Aa phenotype.

<u>Eg:</u> In *Antirrhinum* flowers (زهره حنك السبع) and Carnation flowers(قرنفل)

In the cross between its red and white flowers, all the F_1 generations have **pink flowers** (instead of red in complete dominance). When self-fertilization of F_1, the F_2 ratio was **1 red: 2 Pink: 1 white** (instead of 3 red: 1 white).



Antirrhinum flowers

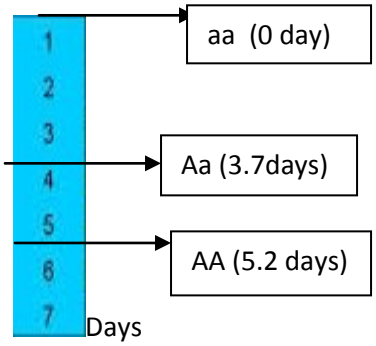
Carnation flowers

2. Partial-Dominance

When the heterozygous (Aa) is **near one** of the homozygous, the dominance is called Partial Dominance.

Eg: Flowering time of peas (blooming time)

The flowering time of homozygous recessive is considered as 0 days (closed flowers) and the flowering time of homozygous dominant (AA) is 5.2 days to open. The heterozygous (Aa) is near one of the homozygous; in this case it is near AA as its flowering time is 3.7 days to open.



Closed flowers

Open flowers

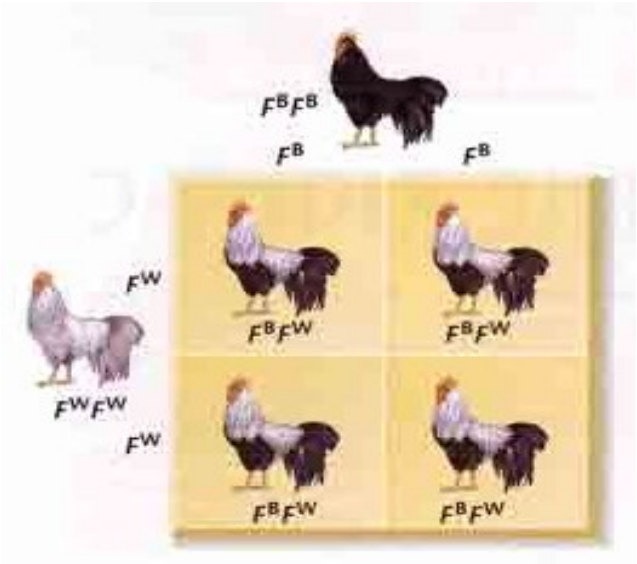
3. Co-dominance (Mosaic Dominance)

Where the alleles forming the genotype of the heterozygous organism is **fully and equally expressed** in phenotype i.e. both the dominant and recessive characters are present. AA phenotype ≠ Aa phenotype.

Eg: <u>a.</u> mosaic of red and white hairs in roan heterozygous shorthorn cattle.

Brown (C^BC^B) Patched (C^BC^W) Brown (C^WC^W)

b. mosaic black and white areas in the Andalusian fowl.



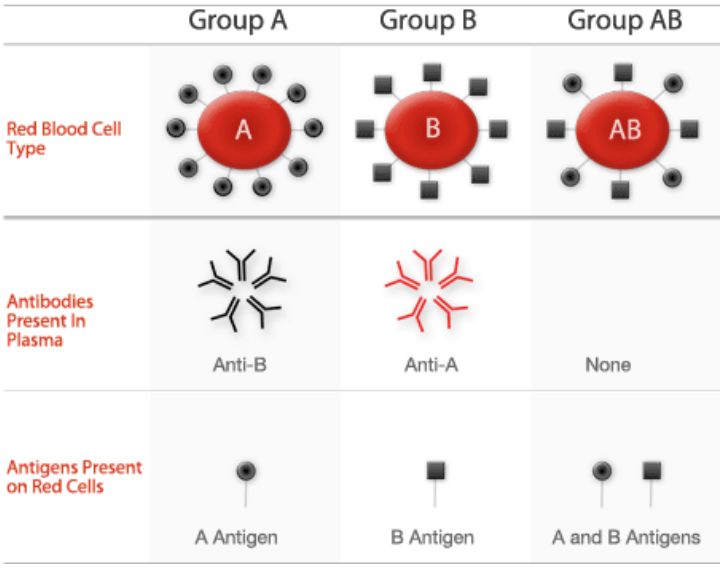
Mixed feather (F^BF^W)

c. mosaic of red and white color of Camellia flowers.

Camellia flower (C^RC^W)

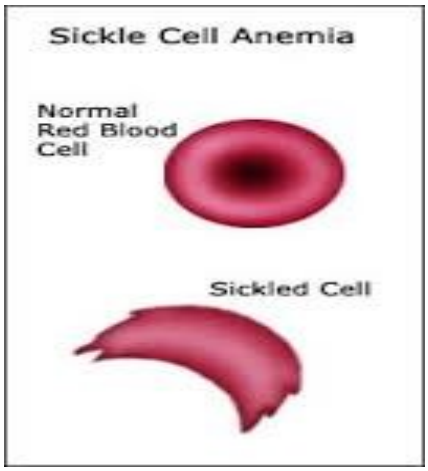
d. AB blood groups

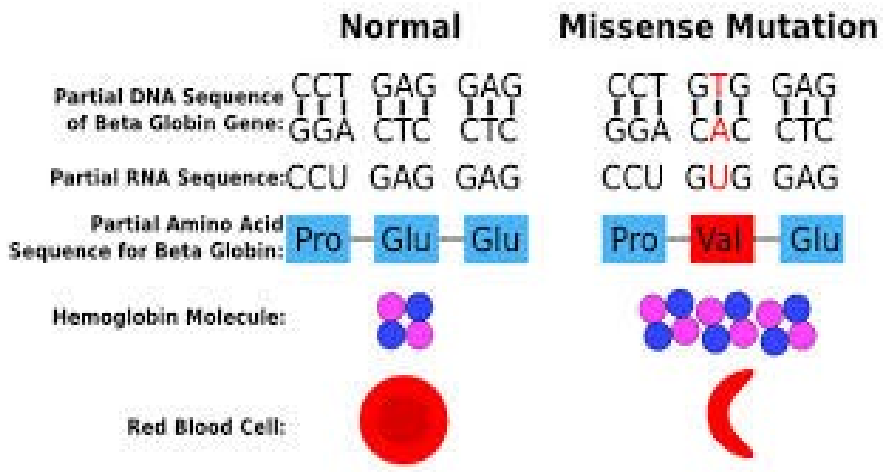
Persons with A blood-type is controlled by I^A allele which synthesis Antigen A, Persons with B blood-type is controlled by I^B allele which synthesis Antigen B, but some persons may have AB blood-type is controlled by both I^A and I^B forming Antigens A and B.



c. Sickle-cell anemia

Persons with *normal discoid biconvex erythrocytes* have the hemoglobin genotype (Hb^A Hb^A); whereas Hb is for haemoglobin and A is for normal erythrocyte, which constitute of normal hemoglobin with glutamic acid (amino acid) group. Person with *sickle-cell anemia* have the heamoglobin genotype (Hb^S Hb^S); whereas Hb is for haemoglobin and S is for Sickle-shaped erythrocyte, which constitute of abnormal hemoglobin with valine amino acid group. In *heterozygous* persons (Hb^A Hb^S); both types of erythrocytes are present in the same time.





Symbolism of No-dominance alleles:

Dominant alleles are usually indicated either by an italic uppercase letter (*D*)

Recessive alleles are usually indicated either by an italic lowercase letter (*d*)

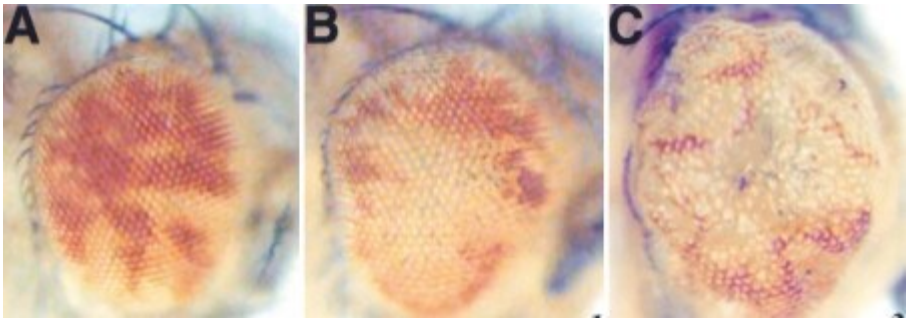
If **no dominance** exists, Capital letters with different superscripts were used to denote alternative alleles i.e. reveal that each allele can express itself in the presence of its alternative in heterozygous.

Eg: Normal haemoglobin allele is $\mathbf{Hb^A}$ and Sickle cell allele is $\mathbf{Hb^S}$

4. Over-Dominance

Where heterozygous organism **may exceeds** the phenotype expression of the homozygous dominant and recessive parents.

Eg: In *Drosophila*; marked increase in the amount of certain fluorescent pigment in heterozygous red-eyed (ww^+, A) comparing with those of the homozygous red-eyed parents ($w^+ w^+$, B) and white-eyed parents (ww,C).



Drosophila eyes

B. Lethal genes

They are caused drastic effect on both structure and function of the organism **causing its death**. Lethal alleles may be **dominant** or **recessive** according to the expression of one or both alleles

1. Dominant lethal genes

They are lethal in heterozygous (Aa) organisms by the effect of a **single dominant allele (A)** i.e. A in Aa genotype. It is rarely considered in genetics, as they are produced by spontaneous mutation and cannot be inherited!? Which makes sense: how can you give an allele to your offspring if you don't survive the prenatal phase.

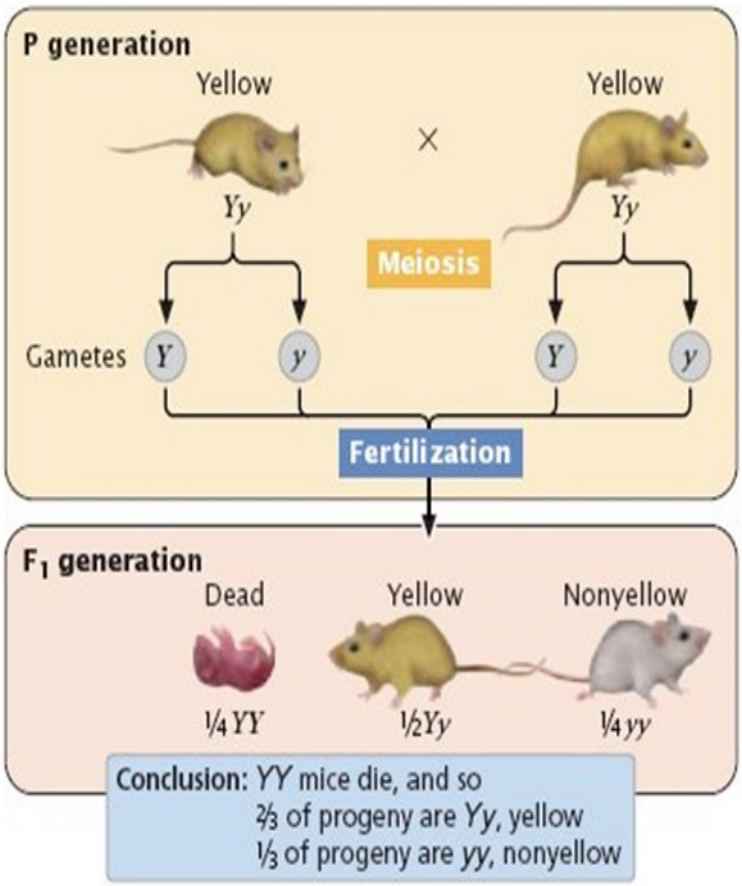
Eg: In *Drosophila*; mutant (irradiated) male may produce sperms carrying dominant lethal allele sperms which will prevent the fertilization of female egg and so, the development of the offspring.

2. Recessive lethal genes

They are **lethal in homozygous individuals** by the effect of both dominant (AA) alleles or recessive alleles (aa).

Eg: (1) In coat color of rats

Yellow color (Yy) is dominant to black coat (yy). The cross of yellow and yellow produce the phenotypic and genotypic ratios 2 yellow (Yy) :1 black (yy) instead of the genotypic ratio 1yellow (YY) :2 yellow (Yy) :1 (yy), fig below. Dissection of pregnant females demonstrated that the YY embryos (1/4 of the offspring) died soon after conception i.e. the allele of yellow color had a dominant phenotype on coat color but at the same time, it had a recessive lethal effects (effect when 2 dominant alleles are present) so, the homozygous yellow YY were invalid.



Coat color of rats

Eg: (2) <u>Sickle cell anemia</u>

They are lethal in homozygous individuals by the effect of both recessive alleles (Hb^sHb^s).

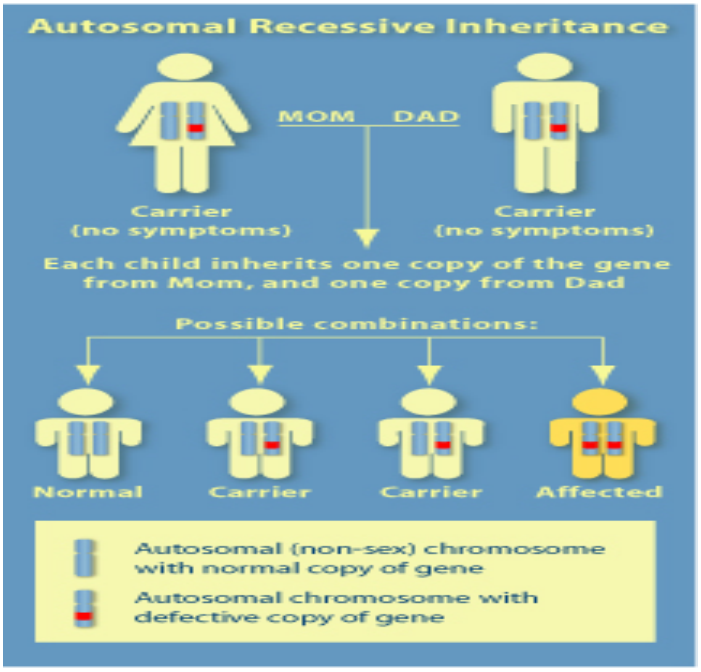
Where, Persons with *normal discoid biconvex erythrocytes* have the hemoglobin genotype ($Hb^A\ Hb^A$); Person with *sickle-cell anemia* have the heamoglobin genotype ($Hb^S\ Hb^S$) and *heterozygous* persons ($Hb^A\ Hb^S$) is a holder for *sickle-cell anemia* disease (Sickle trait حامل المرض).

$Hb^A\ Hb^S$ X $Hb^A\ Hb^S$

$Hb^A\ Hb^A : Hb^A\ Hb^S : Hb^S\ Hb^S$

1(survive): 2 (survive): 1(died)

So, Survival Rate = 1: 2



Eg: (3) <u>Albinism of *Zea* leaf</u>

They are **lethal in homozygous individuals** by the effect of both recessive alleles (cc).

Albinism means the absence of chlorophyll, which lead to the death of seedlings within 2 weeks. Where, (C) represents the dominant allele that control the production of chlorophyll (green seedlings) and (c) represents the recessive allele that causing the absence of chlorophyll (albino seedlings)

So, the cross between heterozygous green *Zea* plants (Cc) will produce offspring with survival ratio of 3 (green) : 0 (albino).

Cc X Cc

CC : Cc : cc

Green: Green: Albino

1(survive): 2 (survive): 1(died)

So, S.R. = 3: 0

C. Multiple Alleles

- In Mendel's experiments, there are one or two kinds of alleles in a gene pair but in some cases the genetic traits are controlled by more than 2 alleles and so called **multiple alleles**. These alleles are the alternative forms for the same gene (performed by mutation) and are distributed among the different individuals, where each individual has only 2 alleles maximum.
- Symbol: A^1, A^2, A^3 or A_1, A_2, A_3 or $A^{\text{the name of character}}$

Eg: (1) In coat color of rabbit

The allele of agouti coat color (C) is completely dominant and albino (c) is completely recessive to agouti (C), chinchilla (c^{ch}) and Himalayan (c^h) alleles.

The relative dominance relationships are $C > c^{ch} > c^h > c$, where:

Agouti (C): banded hairs with gray base, yellow band and black tip,

Chinchilla (c^{ch}): banded hairs with gray base and black tip with no yellow band,

Himalayan (c^h): banded hairs with white base and black tip

and Albino (c): totally white.


Rabbit coat

Rabbit coat color

Allele	Phenotype
C	Rabbit with fully colored coat
c^{ch}	Rabbit with light gray coat
c^{h}	Himalayan rabbit: white with dark ear tips, nose, paws, and tail
c	Albino rabbit

Order of dominance $C \rightarrow c^{ch} \rightarrow c^{h} \rightarrow c$

All the possible genotypes:

$CC,\ Cc^{ch},\ Cc^{h},\ Cc$

$c^{ch}c^{ch},\ c^{ch}c^{h},\ c^{ch}c$

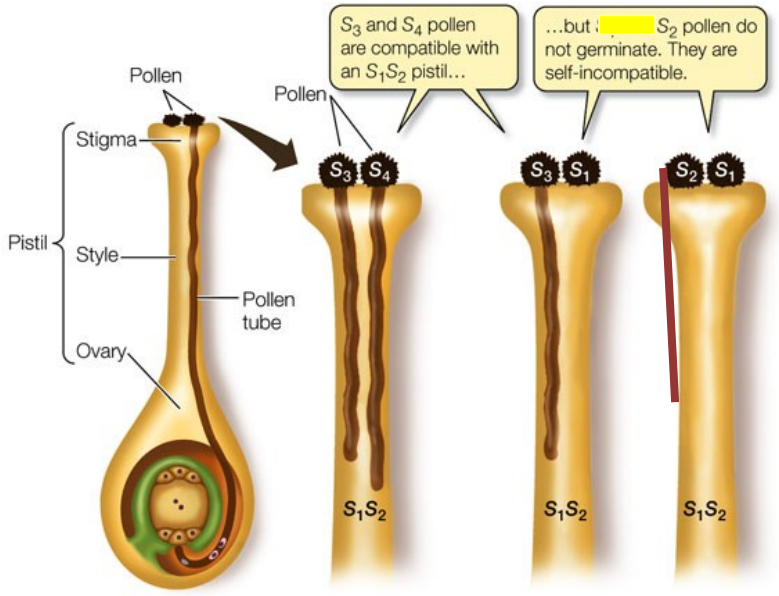
$c^{h}c^{h},\ c^{h}c$

cc

Eg (2). Self-sterility in *Nicotiana tabacum* (tobacco)

In this plant, self-sterility was controlled by a series of multiple alleles called S^1, S^2, S^3,….

A pollen grain carrying a self-sterility allele (S^1) cannot grow (no pollen tube) on its-or any-female style carrying one or both of the same allele (S^1) in its ovules, but successfully fertilize female style of the other types of alleles as S^2, S^3,…



The possible crosses are:

S^1S^1 ♂ and S^1S^1 ♀ produce 100% sterile offspring

S^1S^1 ♂ and S^1S^2 ♀ produce 100% sterile offspring

S^1S^2 ♂ and S^1S^1 ♀ produce 50% sterile : 50% fertile offspring

S^2S^2 ♂ and S^1S^1 ♀ produce 100% fertile offspring

Eg (3) ABO blood groups

Human blood type is an example of both co-dominance and a trait with multiple alleles. ABO blood group is of immense importance. For it is extensively used in blood transfusion in the case of accidents, severe anemia, or surgery etc. Landsteiner was the first to identify such blood groups. The variation in the blood groups is because of the membrane proteins of red blood cells (erythrocytes).

Some of the membrane proteins get glycosylated (addition of sugars) differently thus they produce various types of blood groups. Persons belonging to A blood group contain A type of glycosylated protein in the membrane of erythrocytes. (Similarly "B" and the "O" type). These physiological phenotypes are due to the presence of A, B and O genes controlled by **3 alleles**: $\mathbf{I^A}$ allele which determine

the synthesis of antigen A, $\mathbf{I^B}$ allele which determine the synthesis of antigen B, $\mathbf{I^o}$ **or i** doesn't synthesis either A or B antigens.

Each person will have **TWO** of those alleles (table below).

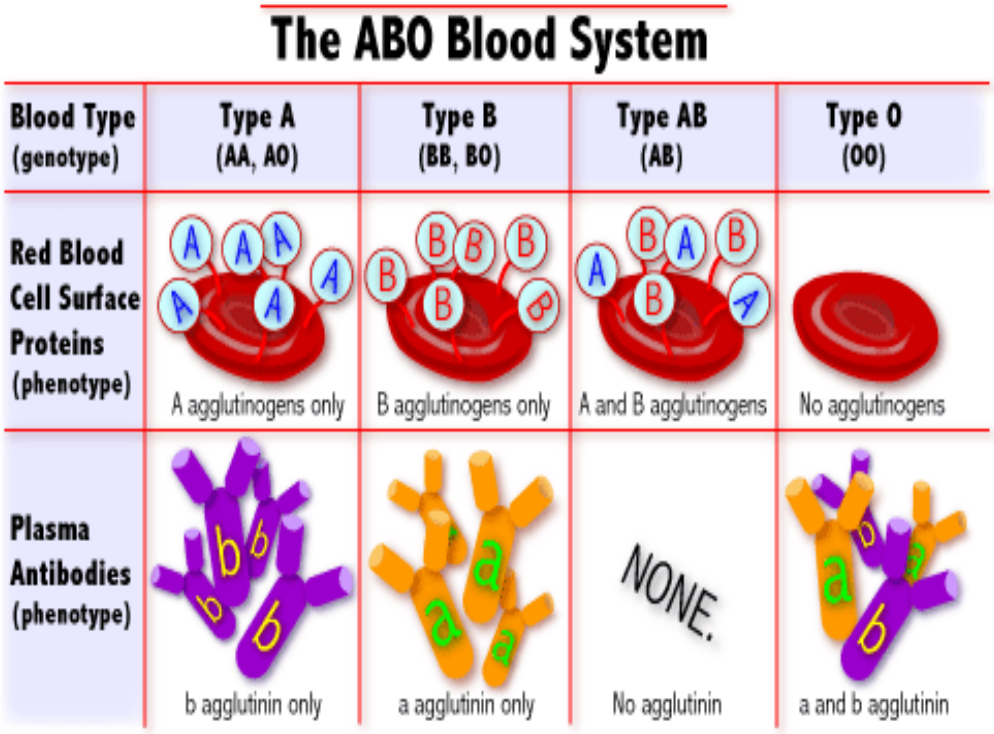
Both A and B alleles dominate the O allele: ($\mathbf{I^A = I^B > i}$)

ABO blood group has **6 genotypes** and **4 phenotypes**: the genotypes of human blood may fall into any of the following 6 types: AA, BB, OO, AB, AO or BO, while the phenotypes of human blood are A, B, AB and O.

Identification of the blood types is very essential for blood transfusion, because, if by chance or mistake, blood of A type is given to B type person or vice-versa, the man who gets such blood type dies because of agglutination or aggregation of blood cells. This aggregation is due to antigen-antibody reaction.

AB blood type is considered as universal acceptor and O blood type is a universal donor.

BLOOD TYPE	GENOTYPE	CAN RECIVE BLOOD FROM
A	I^AI^A (AA) I^Ai (AO)	A, O
B	I^BI^B (BB) I^Bi (BO)	B, O
AB	I^AI^B (AB)	A, B, AB, O
O	ii (OO)	O



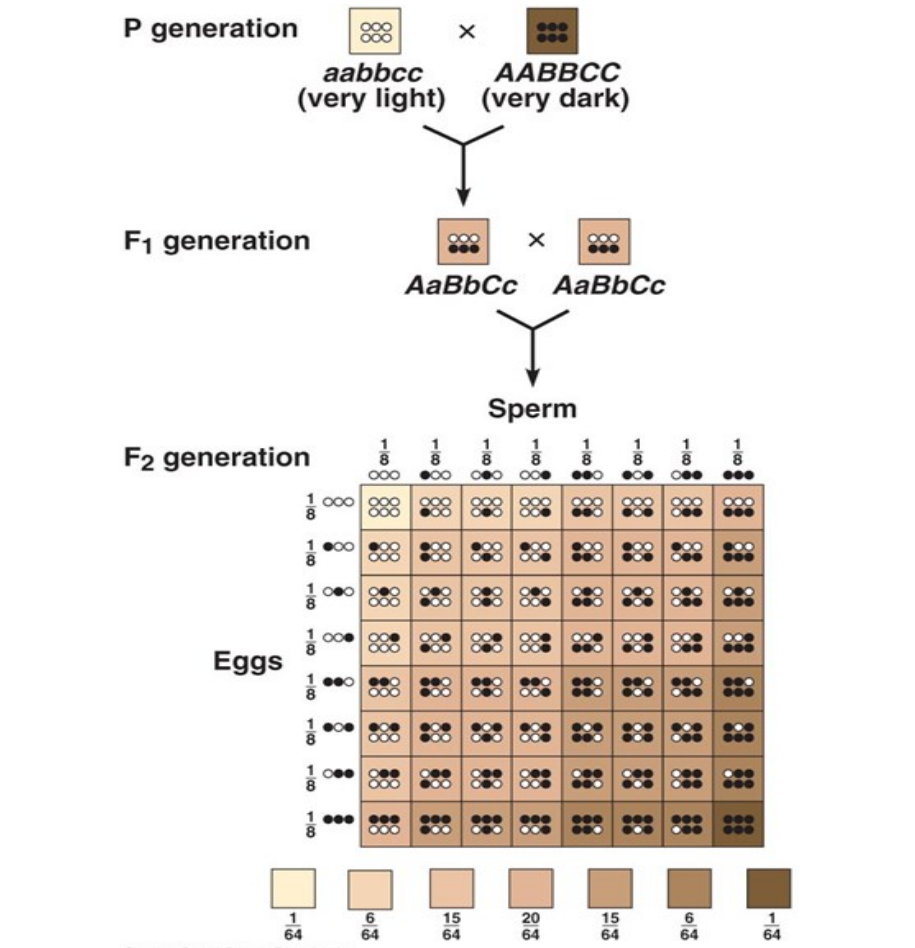
Blood type of cells	Genotype	Antibodies made by body	Reaction to added antibodies	
			Anti-A	Anti-B
A	I^AI^A or I^Ai^O	Anti-B		
B	I^BI^B or I^Bi^O	Anti-A		
AB	I^AI^B	Neither anti-A nor anti-B		
O	i^Oi^O	Both anti-A and anti-B		

LIFE: THE SCIENCE OF BIOLOGY, Seventh Edition, Figure 10.14 ABO Blood Reactions Are Important in Transfusions

Eg (4) Human Skin Color

There isn't a single gene with two alleles for darker brown or lighter white skin; rather, there are multiple alleles for that gene with additive effect, and the

combination you inherit determines your skin color. Suppose one person has black skin and his mate has white, many different combinations are possible, so humans exhibit black skin, white skin, or some shade in between.



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Gene 1	d^1d^1	d^1D^1	d^1D^1	D^1D^1	D^1d^1	D^1d^1	D^1D^1
Gene 2	d^2d^2	d^2d^2	d^2D^2	D^2d^2	D^2d^2	D^2D^2	D^2D^2
Gene 3	d^3d^3	d^3d^3	d^3d^3	d^3d^3	D^3D^3	D^3D^3	D^3D^3
Total number of dark-skin genes	0	1	2	3	4	5	6
	Very light			Medium			Very dark
# of light "d" alleles	6	5	4	3	2	1	0
# of dark "D" alleles	0	1	2	3	4	5	6

FIGURE 10.7 Polygenic Inheritance
Skin color in humans is an example of polygenic inheritance. The dark "D" alleles are found in several different genes and have an additive effect on skin color. The top portion of the figure shows examples of genotypes that can produce the different skin colors. The number of dark "D" alleles is more important than how the "D" alleles are distributed in the different genes.

II. Monogenic inheritance: gene action

In Mendelian principles, each gene pair affects different characters.

Additional works revealed that gene action may be from:

- single alleles that may produce more than one distinguishable unrelated phenotypic effect (**Pleiotropism**)

- segments of the defective genes being doubled in their transmission to children (**Stuttering Alleles)**

3**.** genes or DNA sequences that move from one location to another on a chromosome within the genome sometimes creating or reversing mutations and altering the cell's genome size (**Transposons**).

1. Pleiotropism.

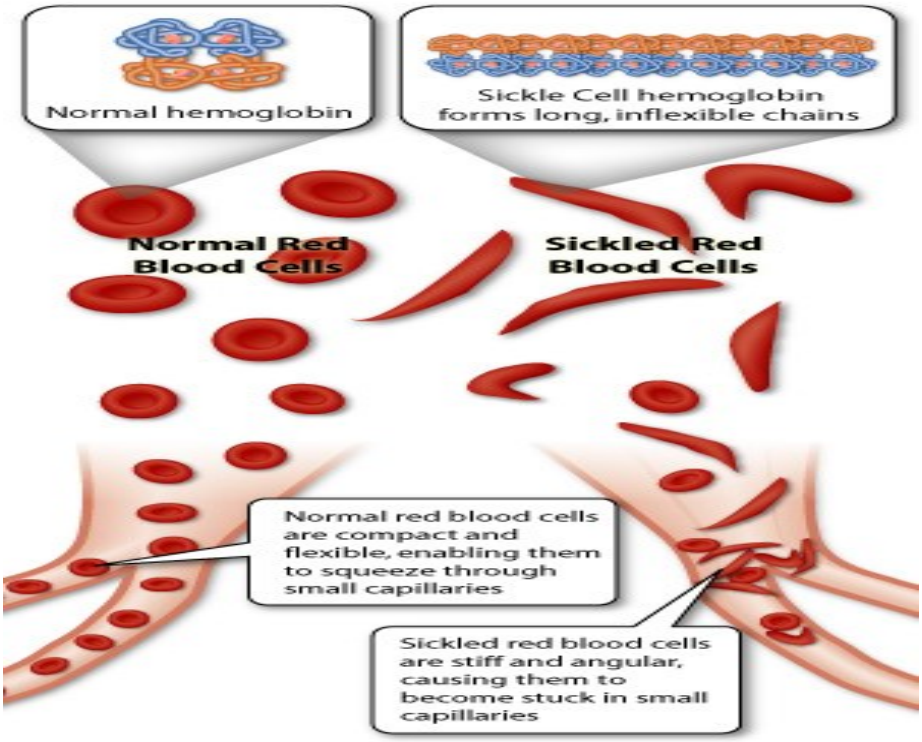
Eg (1): Sickle-cell anemia

The **mutant gene causing abnormal Hb^s hemoglobin** of Hb^SHb^S individuals (have sickle shaped-red blood cells) was followed by more than one phenotypic effect:

i. Deformation of discoid biconvex erythrocytes to sickle-shaped ones which clump and clog the blood vessels.

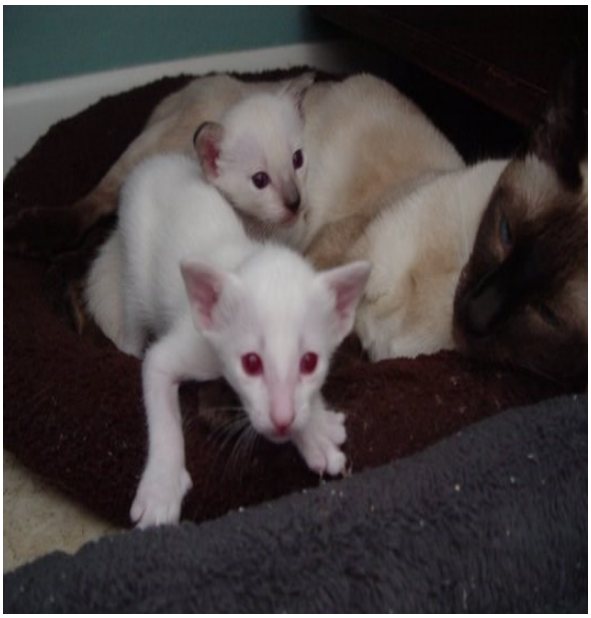
ii. Severe anemia known as sickle-cell anemia

iii. Damage of kidney, spleen, heart and brain.

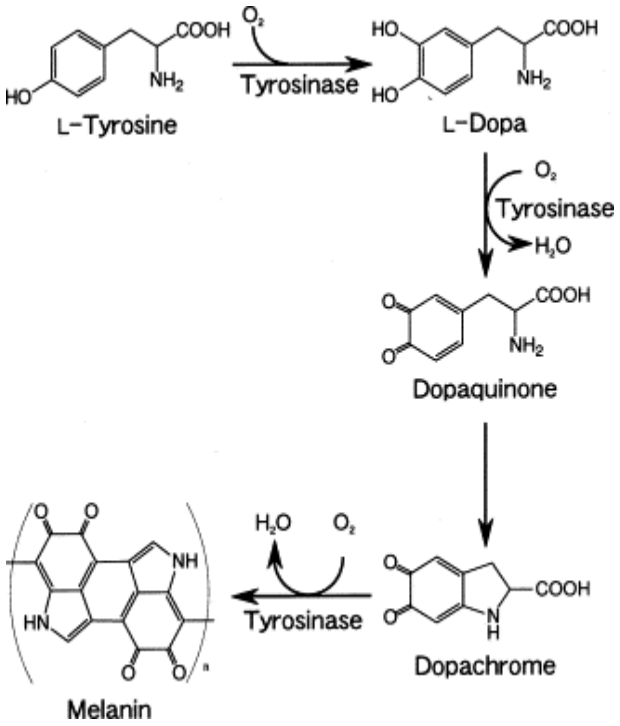


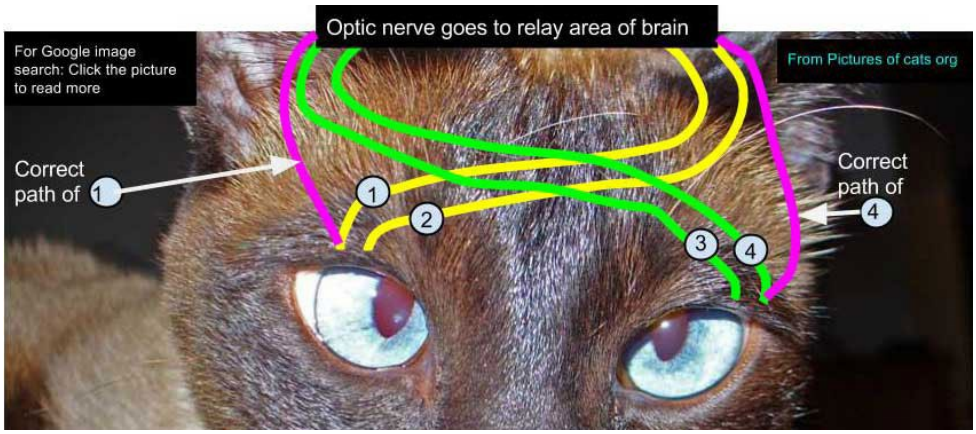
Eg (2): the coloration pattern and crossed eyes of Siamese cats

Both traits are caused by the same allele. This allele produced the same protein (melanin) that control these unrelated characters, but in different cells or during different stages of development as this protein is involved in different metabolic pathways.



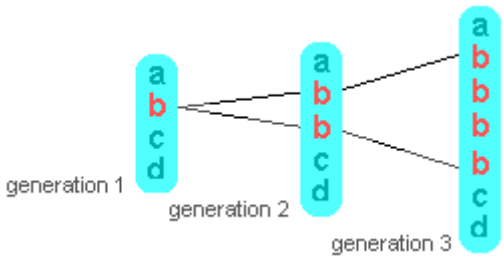
More obscure yet is the connection between melanin synthesis and the formation of a normal optic nerve projection. Siamese kittens are born all-white with **albinism allele** (a form of Himalayan albinism). Albino mutants are known in many mammalian species as in cross-eyed Siamese cats, usually resulting from **mutations of tyrosinase enzyme required for melanin production** (figure below). In embryonic development, melanin tells growing nerves exactly where to go in the eye… with albinism, there is a shortage (or complete lack) of retinal melanin (الميلانين في شبكية العين), but also exhibit incorrect projections from retina to brain (توقعات صحيحة من الشبكية إلى الدماغ), with abnormalities in the optic chiasm (cross the optic nerves) i.e. preventing these kittens from having full normal binocular vision as adults by disruption in the visual pathway and the misrouting of the optic nerve (figure below).





2. Stuttering Alleles

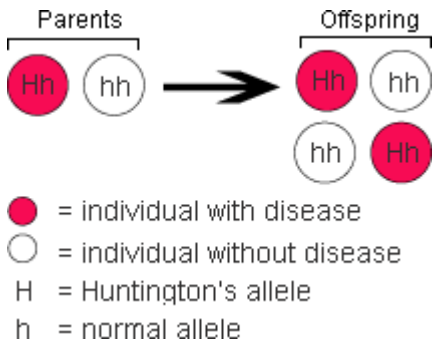
Mendel believed that all units of inheritance are passed on to offspring unchanged **but stuttering alleles or unstable alleles** are an important exception to this rule. Some genetically inherited diseases have more severe symptoms by each succeeding generation due to segments of the defective genes being doubled in their transmission to children (figure below).



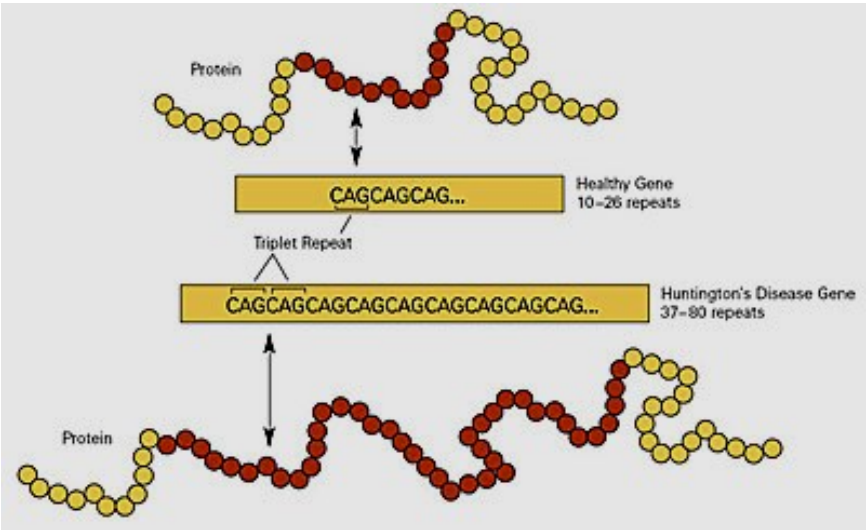
Eg Huntington's disease, fragile-X syndrome, and the myotonic form of muscular dystrophy.

Eg: Huntington's disease

People who inherit **Huntington's disease (HD)** have an abnormal dominant allele that disrupts the function of their nerve cells (neurodegenerative genetic disorder), slowly eroding their control over their bodies and minds and ultimately leading to death of both men and women. The disease is caused by an **autosomal dominant mutation** on one the two copies of the Huntingtin gene (*HTT*), codes for the protein Huntingtin (Htt), so any child of an affected person typically has a 50% chance of inheriting the disease.

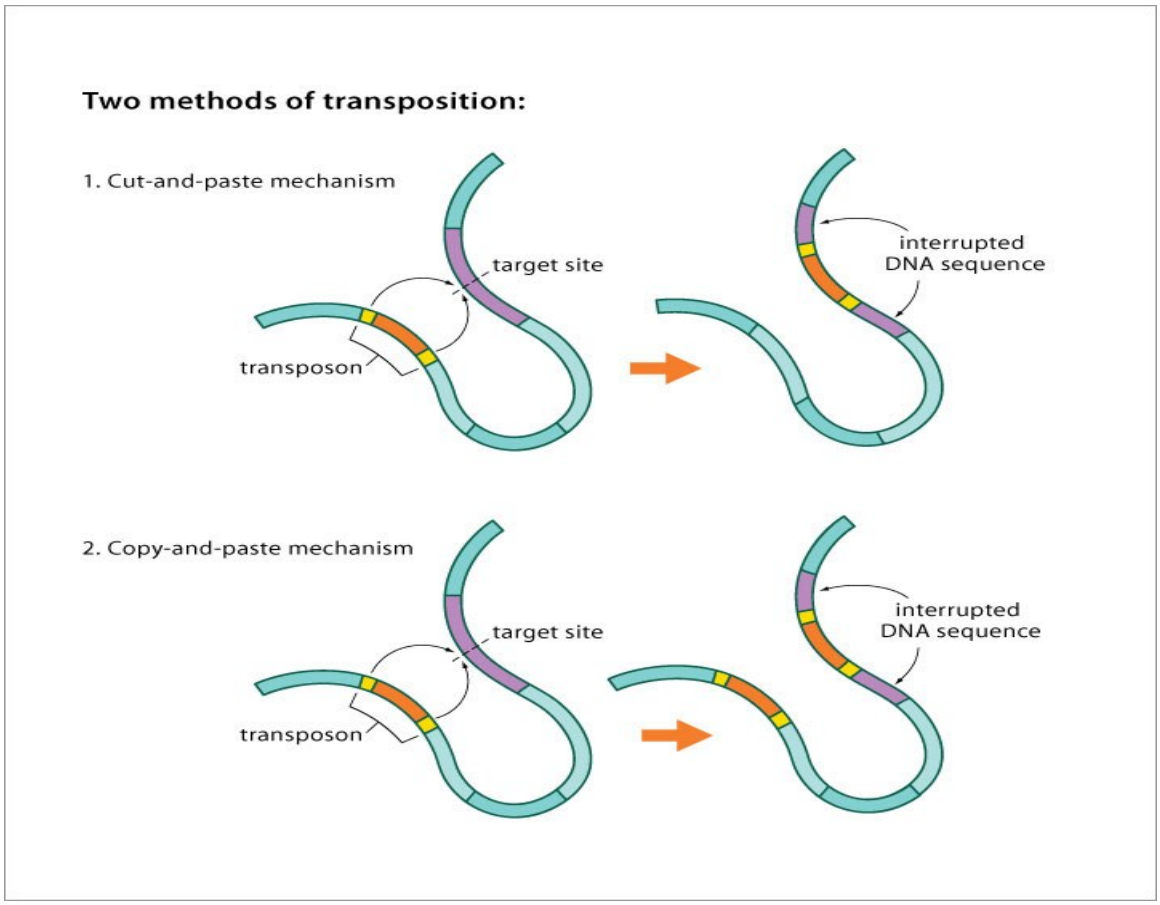


Part of this gene is a repeated section called a trinucleotide repeat, which varies in length between individuals and may change length between generations. **Expansion of a CAG (cytosine-adenine-guanine) triplet repeat stretch within the *Huntingtin* gene** (more than about 35 repeats) results in a different (mutant) form of the protein, which develops the disease and gradually damages cells in the brain, through mechanisms that are not fully understood. If the repeat is present in a healthy gene, a dynamic mutation may increase the repeat count and result in a defective gene. When the length of this repeated section reaches a certain threshold, it produces an altered form of the protein, called mutant Huntingtin protein (mHtt), figure below.



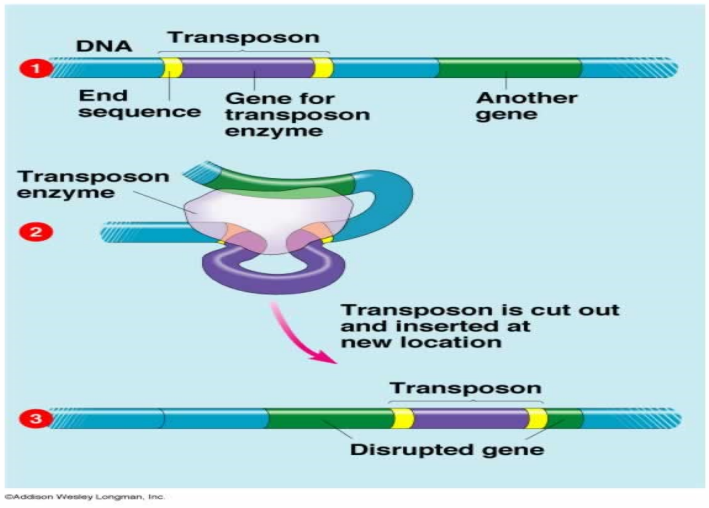
3. Transposons (Jumping genes)

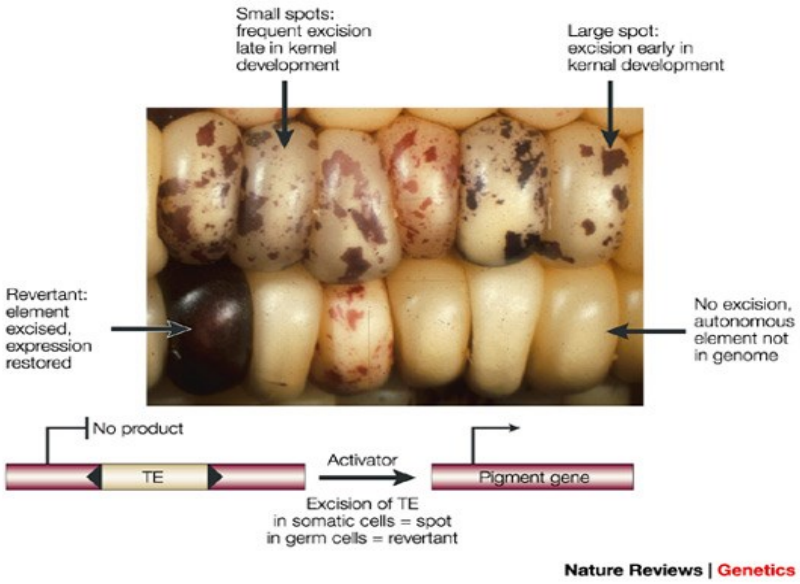
Eg Grains of Indian corn comes in different colors, such as purple, yellow and white. Sometimes the individual grains are purple with white streaks or mottling. This mottling effect defies Mendel's basic principles of genetics because individual grains may be multicolored rather than a single color. The movement of transposons on chromosomes may result in colored, non-colored and variegated grains that do not fit traditional Mendelian ratios based solely on chromosome assortment during meiosis and random combination of gametes. The explanation for this phenomenon involves "**jumping genes" or transposons**, and earned Dr. Barbara McClintock the prestigious Nobel Prize in Medicine in 1983 for her life-long research on corn genetics (mainly chromosome 9).



When a transposon moves to different positions within cells of the corn kernel, the coloration gene is "turned on" or "turned off" depending on whether it lands in a position adjacent to the pigmentation gene:

In the pigmented aleurone layer of corn grains, the position of transposons may inhibits or blocks pigment production in some cells: as if the transposon moves to a position adjacent to a pigment-producing gene, the cells are unable to produce the purple pigment. This results in white streaks or mottling rather than a solid purple grain. The duration of a transposon in this "turned off" position affects the degree of mottling. But if the pigmentation gene is turned off long enough by a transposon, the grain will be completely unpigmented. The reddish-purple patterns caused by transposons may be blotches, dots, irregular lines and streaks.





Additional Knowledge (Read only):

Transposons may also have a profound effect on embryonic development and tumor formation in animal cells. Oncogenes (genes that cause tumors) may be activated by the random reshuffling of transposons to a position adjacent to the oncogene. Transposons may also be useful in genetic engineering with eukaryotic cells, by splicing in transposons to activate certain genes.

III. Polygenic inheritance: gene interaction.

The trait may also be determined by the interaction of **more than one gene** (**Epistasis**), when alleles of one gene pair (**epistatic**) can influence, cover up (mask), or alter the expression of alleles of another gene pair (**hypostatic**). It happens when each gene pair affects a different character. The classical cross between 2 heterozygous give the following genotypes:

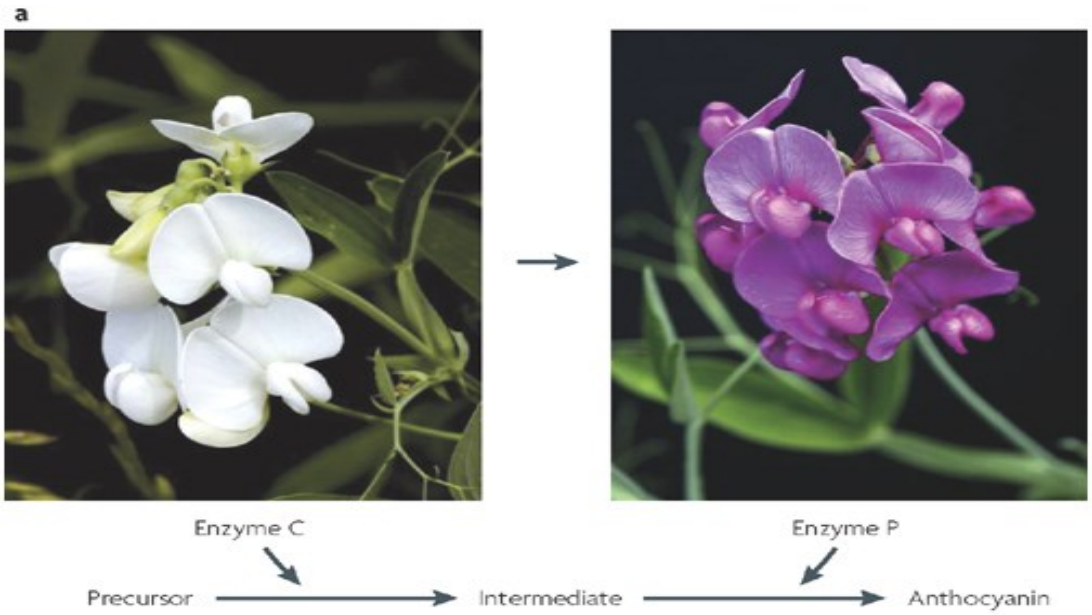
A-B- : A-bb : aaB- : aabb (4 different phenotypes)

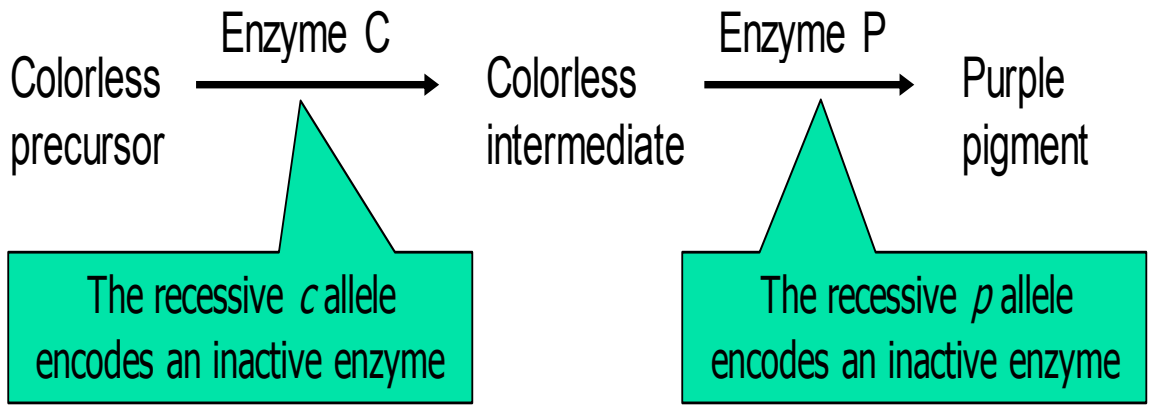
9 3 3 1

The trait is produced through a single pathway and determined by 2 gene pairs, forming **16 offspring** with **less than 4 phenotypes**.

If the two gene pairs affect the same trait, their interaction may modify the above ratio or produce novel phenotypes depending upon the type and degree of interaction.

Genes are usually required to specify the enzymes involved in the **biosynthetic pathways** that transfer the original substance to the end product. Gene interaction occurs whenever 2 (or more) genes form enzymes which catalyze steps in a common pathway. Eg: Flower color in Sweet Pea





Two genes are responsible for the chemical reaction that produces the plant pigment anthocyanin from a precursor molecule. Gene C controls the first step in the reaction to produce the step 1 product, and gene P controls the second step in the reaction to produce anthocyanin. These genes control flower color by controlling pea plant biochemistry, in particular that related to pigment compounds called anthocyanins. In peas, there is a two-step chemical reaction that forms anthocyanins; gene *C* is responsible for the first step, and gene *P* is responsible for the second. If either step is nonfunctional, then no purple pigment is produced, and the affected pea plant bears only white flowers. The dominant *C* and *P* alleles code for functional steps in anthocyanin production, whereas the recessive *c* and *p* alleles code for nonfunctional steps. Thus, if two recessive alleles occur for either gene, white flowers will result.

Genes reveal different epistatic relations:

1. Recessive epistasis (9:3:4)

The homozygous recessive gene (aa) is masking the other dominant gene (B-, Bb or BB). This mean that the character of (aa) in any genotype appear while that of (B-) is masked.

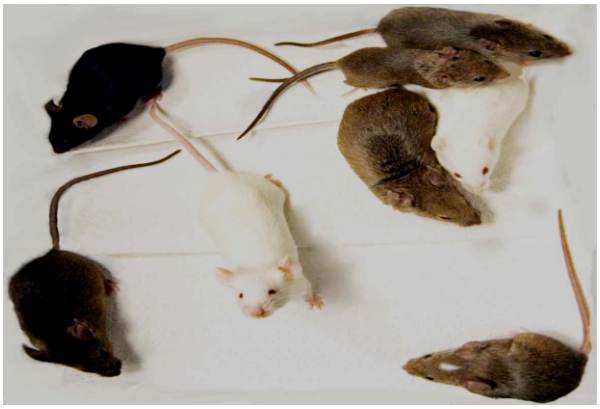
Eg: Skin color of house mouse

Crossing AABB x aabb or AAbb x aaBB will have F_1 AaBb and F_2 will have a ratio 9:3:4, where A=black, B=yellow band, aa or bb=albino.

A-B- (Agouti) : A-bb (Black) : aaB- (Albino) : aabb (Albino)

9 3 (3 + 1)

9 3 4



2. Duplicate recessive epistasis (9:7)

Either homozygous recessive gene (aa or bb) produce the same phenotype by masking over either dominant gene (B- as Bb and BB or A- as AA and Aa). This mean that the character of aa and bb in any genotype appear while that of (B-) and (A-) is masked.

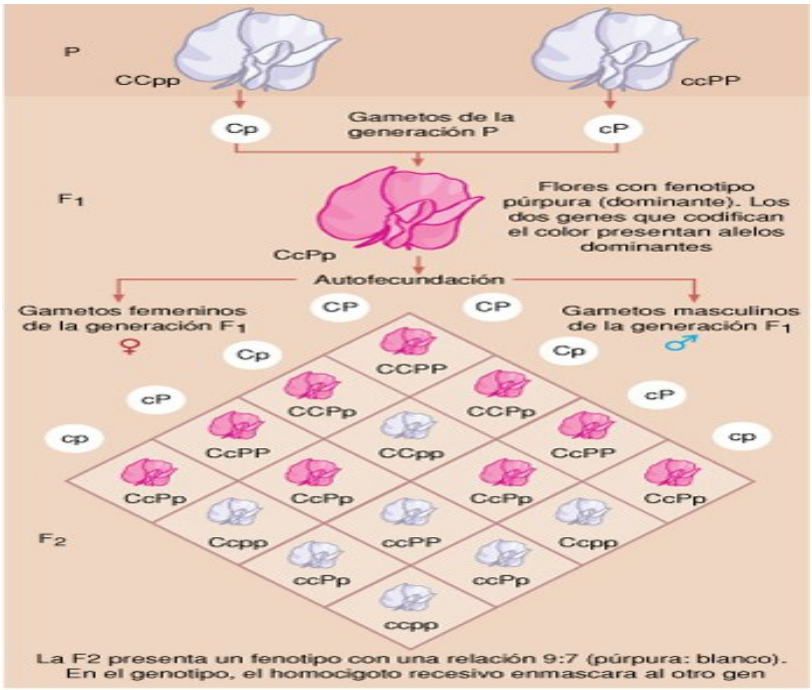
Eg: Flower color of sweet pea (*Lathyrus*)

Crossing AABB x aabb or AAbb x aaBB will have F_1 AaBb and F_2 will have a ratio 9:7, where A=Pink, B=Pink, aa or bb=white.

A-B- (Pink) : A-bb (white) : aaB- (white) : aabb (white)

9 (3 + 3 + 1)

9 7



(b) A dihybrid cross involving complementary gene action

P: *AA bb* × *aa BB*

Gametes: *A b* , *a B*

F_1 (all identical): ♀*Aa Bb* × ♂*Aa Bb*

F_2

	A B	*A b*	*a B*	*a b*
A B	*AA BB*	*AA Bb*	*Aa BB*	*Aa Bb*
A b	*AA Bb*	*AA bb*	*AaBb*	*Aa bb*
a B	*Aa BB*	*Aa Bb*	*aa BB*	*aa Bb*
a b	*Aa Bb*	*Aa bb*	*aa Bb*	*aa bb*

9	*A– B–*(purple)
7	(3)*A– bb* (3)*aa B–* (1)*aa bb* (white)

(c) A biochemical model for purple pigment production

Colorless precursor 1 → (Allele *A*: Pigment change initiated) → Colorless precursor 2 → (Allele *B*: Pigment change completed) → Purple pigment

3. Dominant epistasis (12:3:1)

One dominant gene (A) is masking the other dominant gene (B-, Bb or BB). This mean that the character of A in any genotype appear while that of B- is masked.

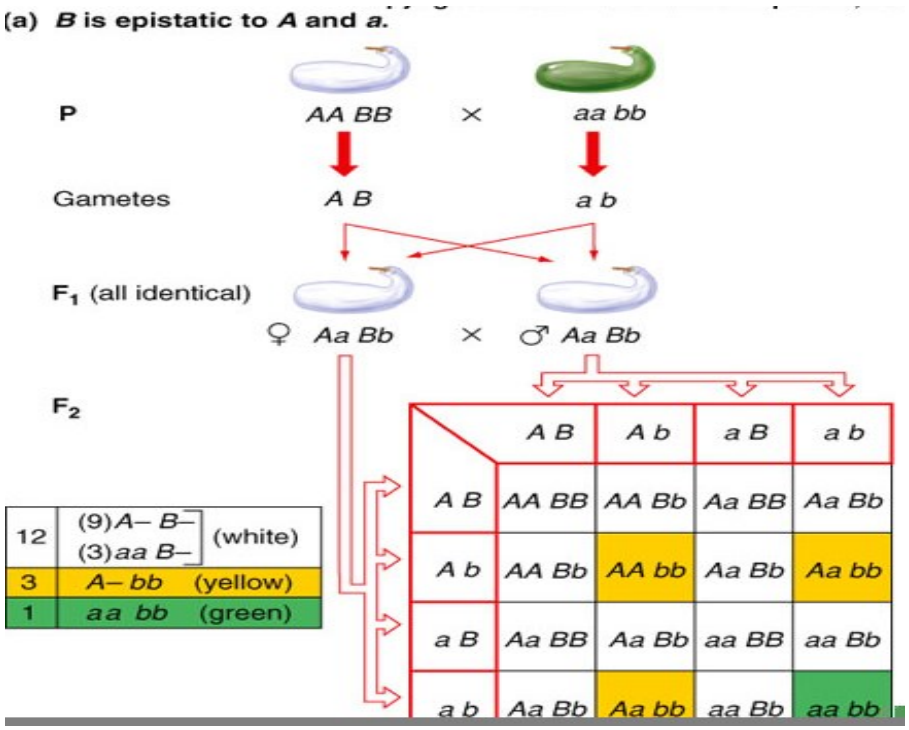
Eg: Fruit color of *Cucurbita*

Crossing AABB x aabb or AAbb x aaBB will have F_1 AaBb and F_2 will have a ratio 12:3:1, where A=white, B=yellow, aa or bb=green.

A-B- (white) : A-bb (white) : aaB- (yellow) : aabb (green)

(9 + 3) 3 1

12 3 1



4. Duplicate dominant epistasis (15:1)

The dominant alleles of either or both genes (A, B, AB) produce the same phenotype by masking over either recessive genes (bb or aa). This mean that the character of A-, B- and A-B- genotype appear while that of (aa) and (bb) is masked.

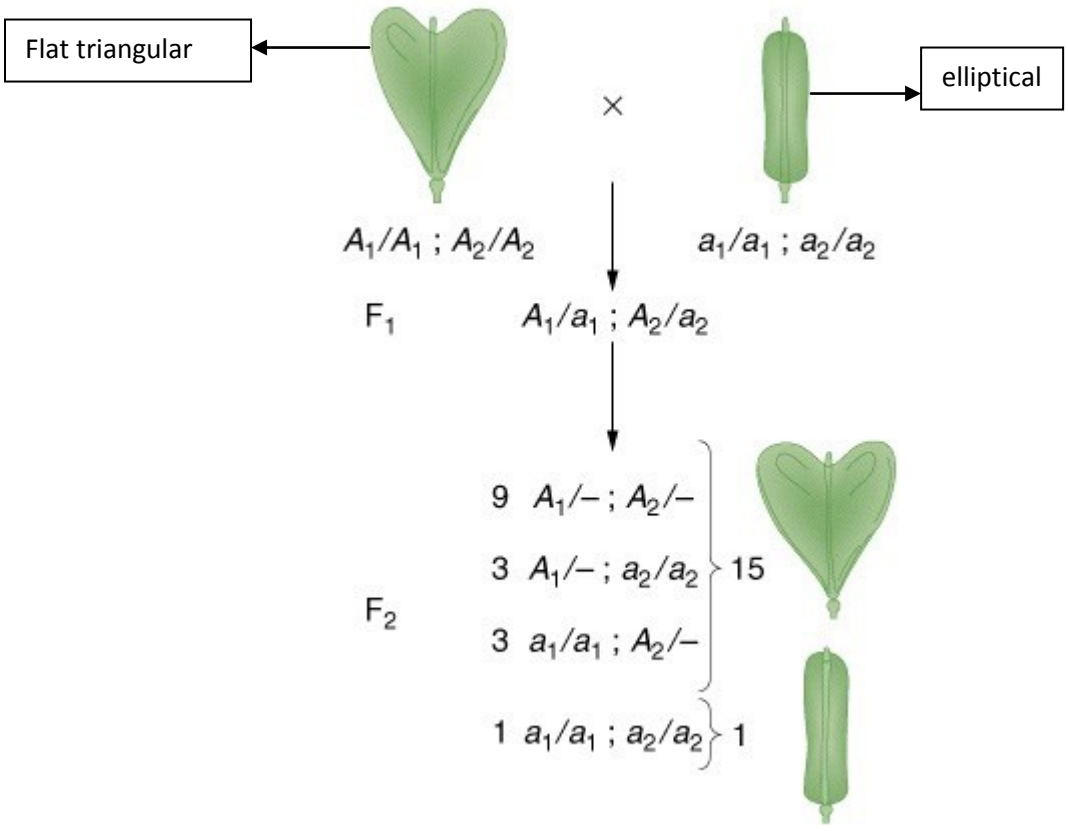
Eg: Fruit shape of *Capsella*

Crossing AABB x aabb or AAbb x aaBB will have F_1 AaBb and F_2 will have a ratio 15:1, where A=B=Flat triangular, aa or bb=elliptical.

A-B-(FlatTri.): A-bb (FlatTri.):aaB- (FlatTri.): aabb (elliptical)

(9 + 3 + 3) 1

15 1



5. Dominant and Recessive epistasis (13:3)

The homozygous recessive gene (aa) and the dominant allele of the other gene (B-) are masking the related dominant gene (A-, Aa or AA) or homozygous

recessive of the other (bb). This mean that the character of (aa and B-) in any genotype appear while that of (A- and bb) is masked.

Eg: Feather color of domestic fowls

Crossing AABB x aabb or AAbb x aaBB will have F_1 AaBb and F_2 will have a ratio 13:3, where A=bb=colored feather, B= aa=white.

A-B- (white) : A-bb (colored) : aaB- (white) : aabb (white)

3

13

Note:

When either or both dominant genes (A) and (B) affect the same trait in the same way, they are termed **Duplicate genes**. But when the dominant gene (B) inhibits the effect of the dominant gene (A), they are termed **Inhibiting genes**.

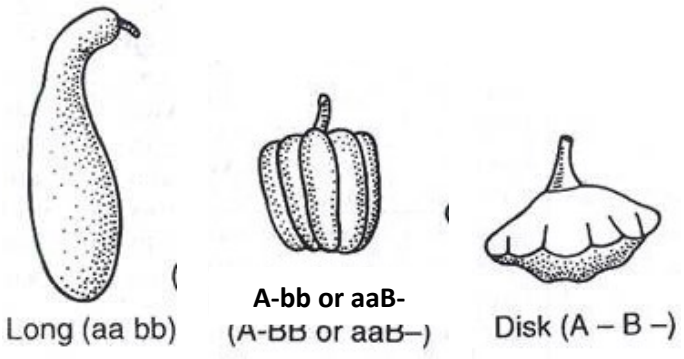
6. Duplicate genes with cumulative effect تاثير تراكمى (9:6:1)

Certain phenotypic traits depend on the dominant alleles of two gene loci. When dominant is present it will show its phenotype. The ratio will be 9: 6: 1. Complete dominance at both gene pairs, interaction between both dominance to give new phenotypes.

Eg: Fruit shape in summer squash

Gene pair 'A' sphere shape dominant over long one.

Gene pair 'B' sphere shape dominant over long one.



Interaction at 'AB' when present together, form disc-shaped fruit

Disc shaped fruits 9/16 : Sphere shaped fruits 6/16 : Long shaped fruit 1/16

Sphere shape × Sphere shape
AAbb aaBB
AaBb × AaBb
Disc shape ↓ disc shape

AB = 9 Disc shape
Ab = 3 = Sphere shape
aB = 3 = Sphere shape
ab = 1 = Long shape
= 9 : 6 : 1
Disc Sphere Long

	AB	Ab	aB	ab
AB	AABB Disc	AABb Disc	AaBB Disc	AaBb Disc
Ab	AABb Disc	AAbb Sphere	AaBb Disc	Aabb Sphere
AB	AaBB Disc	AaBb Disc	aaBB Sphere	aaBb Sphere
ab	AaBb Disc	Aabb Sphere	aaBb Sphere	aabb Long

Students guide: When you study epistasis perform a table consisting of name, ratios, whose gene (or allele) mask whome?

III. Sex related gene: Sex-linked, sex influenced and sex limited

Many organisms have homologous pairs of all chromosomes except for those that determine sex. The chromosomes that occur as homologous pairs in all organisms of a species are called **autosomes**. Chromosome pairings that can vary depending on the sex of an organism are called **sex chromosomes**. In most vertebrates, including humans, females with XX have two copies for X-linked genes; On the other hand, XY males are one copy (hemizygous) with respect to the genes present on the different X and Y chromosome. In humans, there are hundreds of genes located on the X chromosome that have no counterpart on the Y chromosome. X-linked inheritance diseases are single gene disorders that reflect the presence of defective genes on the X chromosome.

There are three categories of genes that may have different effects depending on an individual's gender. These are referred to as:

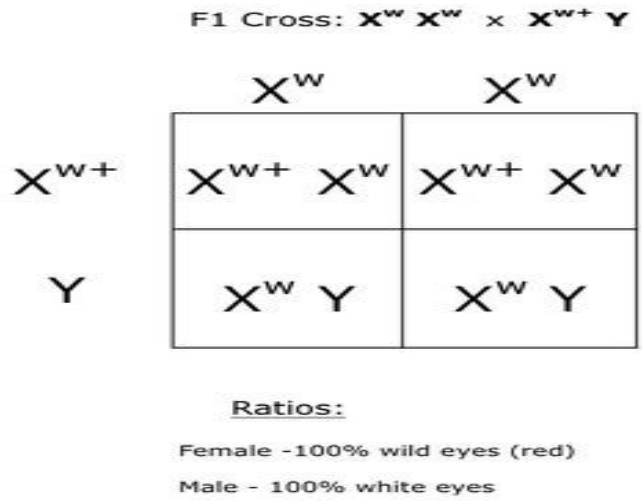
1. sex-linked genes 2. sex-limited genes 3. Sex-influenced

2. Sex-linked inheritance:

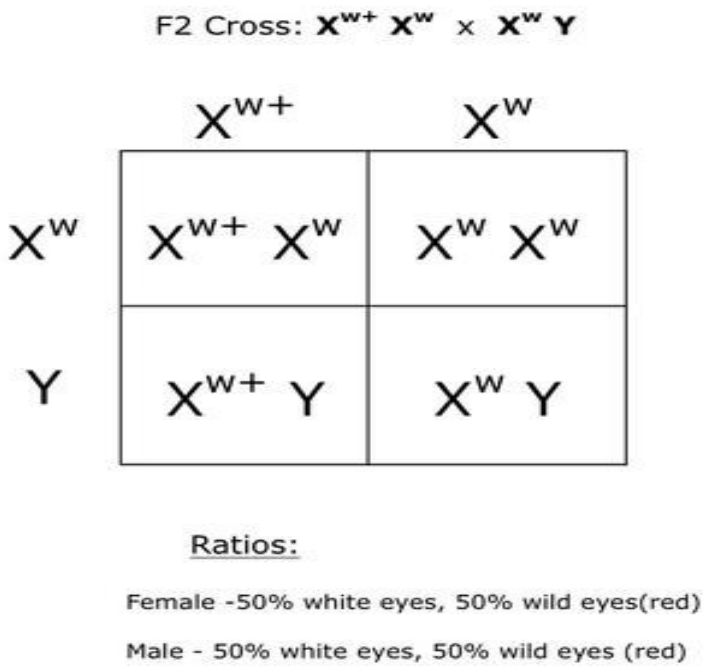
Gene located on the sex chromosomes are said to be sex-linked and have different patterns of inheritance.

- The eye color in *Drosophila* is X-linked with the gene for wild red-eyes (w+) being dominant over the white-eyed gene (w).

By crossing white-eyed females and red-wild eyed males (genotypes $X^w X^w$ and $X^{w+}Y$). Since the wild red-eye gene is dominant, the result of this cross was all wild eyed are females and white eyed are males (F_1).



By crossing, the wild-red eyed females and white-eyed males from the F_1 generation. The expected result would be a 1:1 ratio of wild red-eyes to white eyes for both male and female flies.



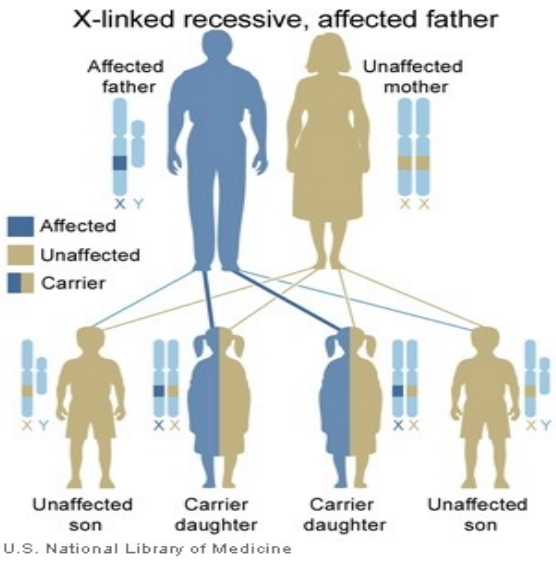
The inheritance patterns of X-linked diseases in family pedigrees (cross) are complicated and can be either recessive or dominant. The X-linked dominant diseases are very uncommon, but X-linked recessive diseases are much more frequent and include Duchenne and Becker forms of muscular dystrophy ضمور العضلات and hemophilia, as well as red-green color blindness.

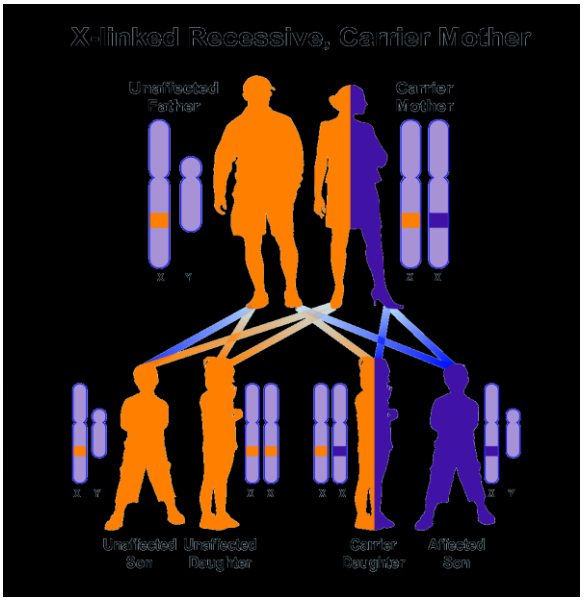
These diseases are much more common in males than females because two copies of the mutant allele are required for the disease to occur in females, while only one copy is required in males so, they express the genes it contains whether they are dominant or recessive.

The inheritance pattern of an X-linked recessive disease has the following unique characteristics:

(1) Males always pass their X chromosome to their daughters but never to their sons (no father-to-son transmission) since sons will inherit the Y rather than the X chromosome. Affected males pass the defective X chromosome to all of their daughters, who are described as obligate carriers. This means they carry the disease-causing allele but generally show no disease symptoms since a functional copy of the gene is present on the other chromosome.

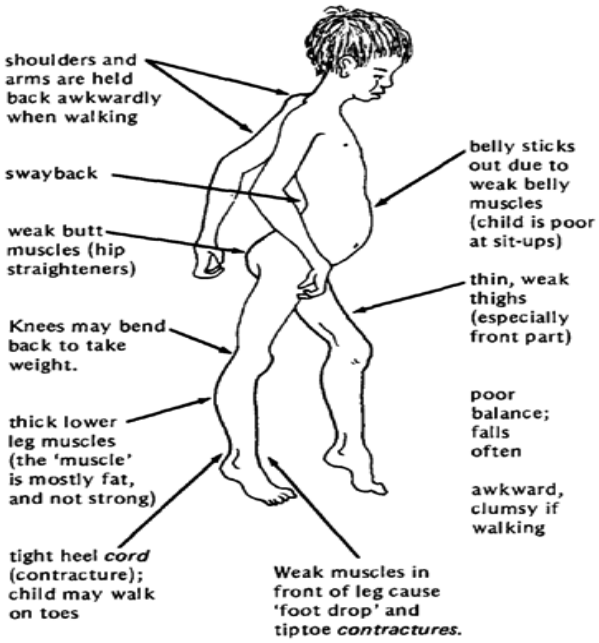
(2) The carrier females (heterozygote) have a 50 percent chance of passing the mutant gene to each of her children (daughters and sons). Female carriers pass the defective X chromosome (mutant X gene) to half their sons (who are affected by the disease, known as **hemizygotes**) which express the trait and half their daughters (who are therefore also carriers). The other children inherit the normal copy of the chromosome.





Eg (1): Duchenne and Becker forms of muscular dystrophy

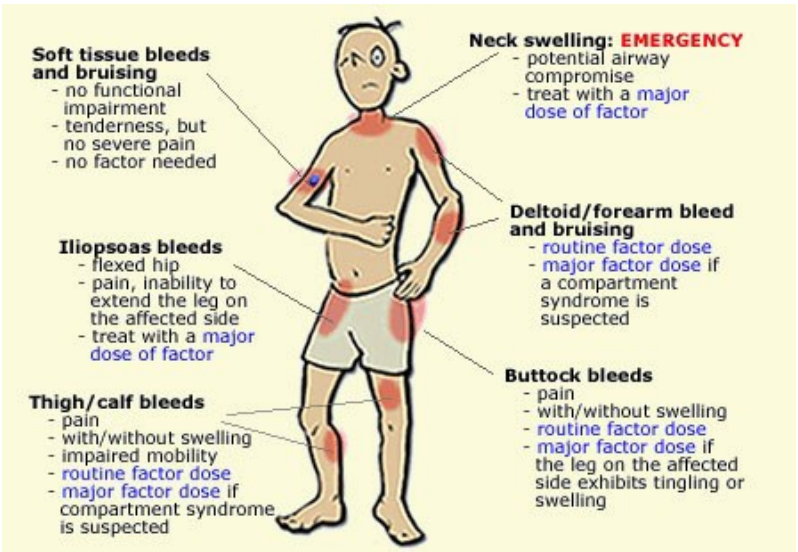
It is a type of dystrophinopathy, which includes a spectrum of muscle diseases in which there is insufficient dystrophin produced in the muscle cells, resulting in instability in the structure of muscle cell membrane. This is caused by mutations in the dystrophin gene, which encodes the protein dystrophin. Becker muscular dystrophy (BMD) is related to Duchenne muscular dystrophy (DMD) in that both result from a mutation in the *dystrophin* gene, but in Duchenne muscular dystrophy no functional dystrophin is produced making DMD much more severe than BMD.



Muscular dystrophy

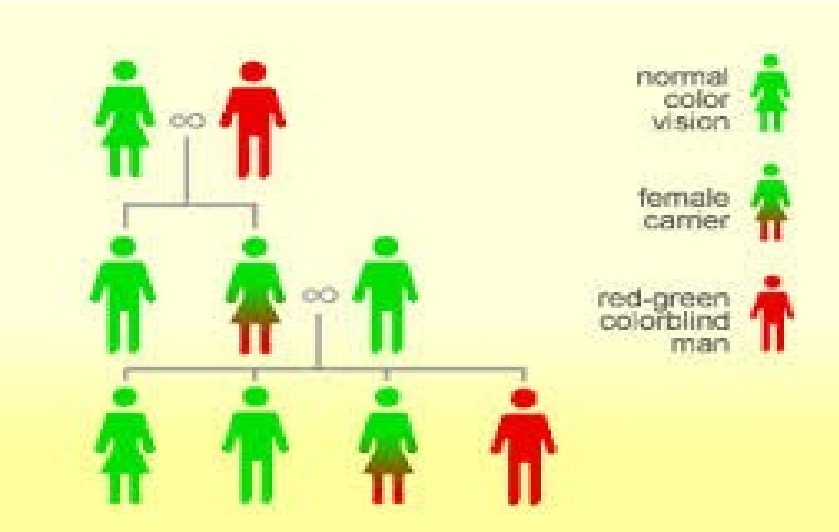
Eg (2): Hemophilia

It is a group of hereditary genetic disorders that impair the body's ability to control blood clotting or coagulation, which is used to stop bleeding when a blood vessel is broken. Haemophilia A (clotting factor VIII deficiency) is the most common form of the disorder, present in about 1 every 5,000–10,000 male births. Haemophilia B (factor IX deficiency) occurs in around 1 every 20,000–34,000 male births.

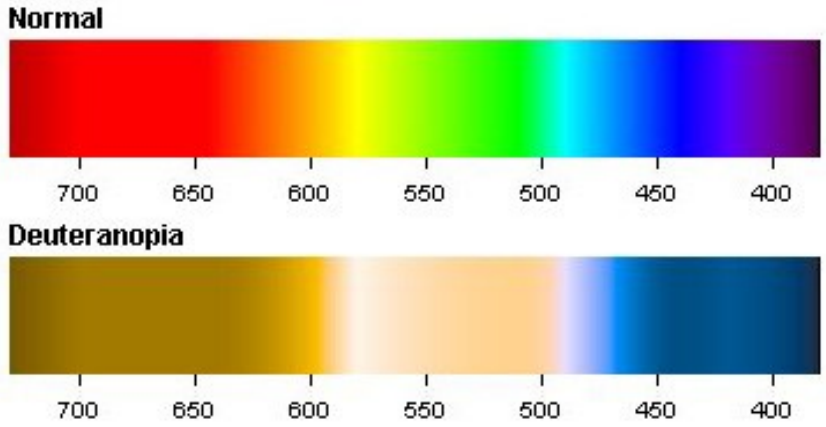


Eg (3): Red-green color blindness:

Color blindness, or **color vision deficiency (**deuteranopia) is the inability or decreased ability to see color, or perceive color differences, under normal lighting conditions as red and green are the main *problem* colors. Color blindness affects a significant percentage of the population. There is no actual blindness but there is a deficiency of color vision. The most usual cause is a fault in the development of one or more sets of retinal cones that perceive color in light and transmit that information to the optic nerve. The genes that produce photopigments are carried on the X chromosome; if some of these genes are missing or damaged, color blindness will be expressed in males with a higher probability than in females because males only have one X chromosome (in females, a functional gene on only one of the two X chromosomes is sufficient to yield the needed photopigments).



The English chemist John Dalton published the first scientific paper on this subject in 1798, "Extraordinary facts relating to the vision of colours", after the realization of his own color blindness.



Normal and color blindness Spectrum

Pedigree (cross) for all X-linked recessive disease:

P XX X^cY

Normal Diseased

↓

F1 XX^c XY

50% ♀ carrier : 50% ♂normal

P XX^c XY

Carrier Normal

↓

F1 XX XX^c XY X^cY

25% ♀ normal : 25% ♀carrier : 25% ♂ normal : 25% ♂ diseased

P XX^c X^cY

Carrier Diseased

↓

F1 XX^c X^cX^c XY X^cY

25% ♀ carrier : 25% ♀ Diseased : 25% ♂ normal : 25% ♂ Diseased

P X^cX^c (Diseased) X^cY (Diseased)

↓

F1 X^cX^c X^cY

50% ♀ Diseased : 50% ♂ Diseased

(so, 100% diseased)

The difference between the 3 diseases will be the superscript sign: **d** for Duchenne and Becker forms of muscular dystrophy, **h** for Hemophilia and **c** for color blindness.

3. **Sex-limited inheritance**: They are autosomal genes (genes located on autosome chromosomes, i.e. not located on the sex chromosomes) that are expressed only in males or females, but not both (i.e. expressed in only one sex and 'turned off' in the other).

   - Sex organs production **in Human**: Sperm in testes for males (♂) and egg in ovary for females (♀).

   - **In Chicken**, the production of egg is performed by Hen not by Rooster.
   - Feathering way of Rooster differs from Hen (Males of most chicken breeds distinguish from their females in having longer, sharp and more scalloped feathers in neck, hackle, saddle and wing bows).

- The genes that control milk yield and quality **in mammalians**; for example it is present in both bulls (♂) and cows (♀), but their effects are expressed only in the female cattle.

4. **Sex-influenced inheritance**: Traits are autosomal, meaning that their genes are not carried on the sex chromosomes but are inherited by males and females and appear in both, but normally differ in how the phenotypes are expressed as the trait is dominant in men while at the same time it is recessive in women.

   Eg **Patterned baldness** is controlled by the same allele pair in both sexes, but the allele is dominant in males and recessive in females. Obviously other factors (genes) are involved in the expression of this trait.

Pedegree (cross):

P **XX** **X^RY**

Normal **Baldness**

↓

F1 **X^RX** **XY**

50% ♀ carrier : 50% ♂normal

P **XX^R** **XY**

Carrier **Normal**

↓

XX **XX^R** **XY** **X^RY**

25% ♀ normal : 25% ♀ carrier : 25% ♂ normal : 25% ♂ Baldness

P **XX^R** **X^RY**

Carrier **Baldness**

↓

F1 **XX^R** **X^RX^R** **XY** **X^RY**

25% ♀ carrier : 25% ♀ Baldness : 25% ♂ normal : 25% ♂ Baldness

P X^RX^R X^RY
Baldness Baldness
↓
F1 X^RX^R X^RY
50% ♀ Baldness : 50% ♂ Baldness
(so, 100% Balness)

P X^RX^R XY
Baldness Normal
↓
F1 X^RX X^RY
50% ♀ Carrier : 50% ♂ Baldness

IV. Cytoplasmic inheritance

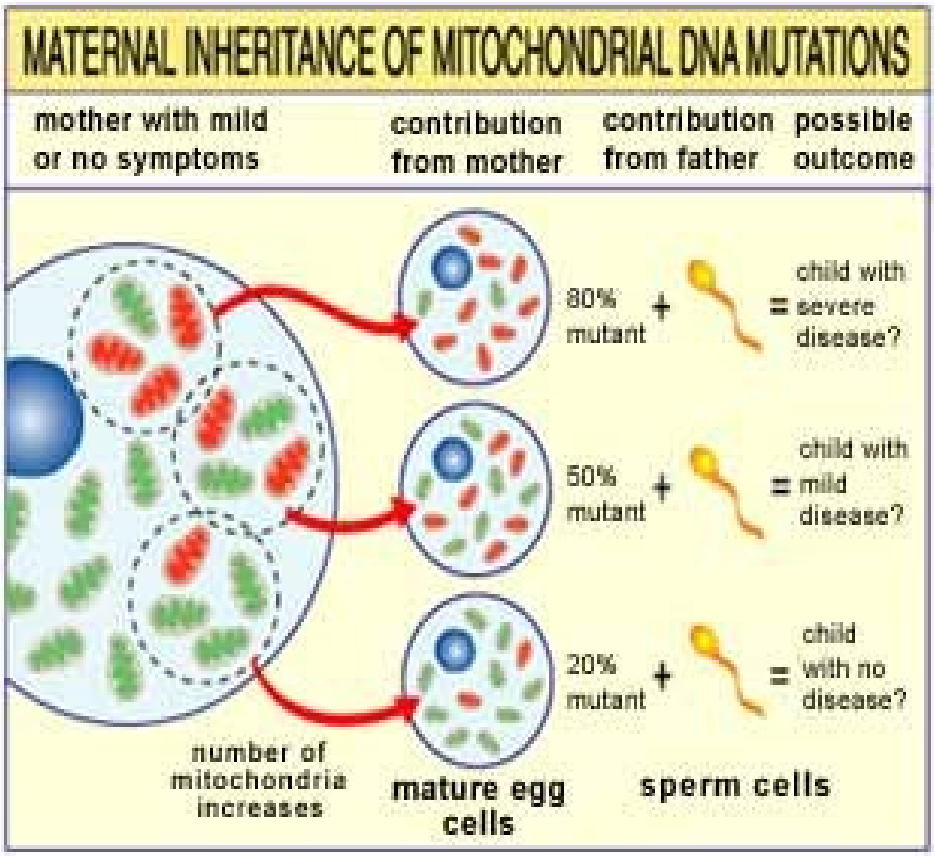
Extranuclear inheritance or **cytoplasmic inheritance** is the transmission of genes that occur outside the nuclear chromosomes i.e. from mitochondrial DNA or chloroplast DNA. It is found in most eukaryotes and is commonly known to occur in cytoplasmic organelles such as mitochondria and chloroplasts.

Extranuclear Inheritance of Organelles

Mitochondria are organelles which function to produce energy as a result of cellular respiration of human, plants, …. Chloroplasts are organelles which function to produce sugars via photosynthesis in plants and algae. The genes located in mitochondria and chloroplasts are very important for proper cellular function. The extranuclear genomes of mitochondria (mt DNA) and chloroplasts (ct DNA or cp DNA) however replicate independently of cell division. They replicate in response to a cells increasing energy needs which adjust during that cells lifespan.

Both chloroplasts and mitochondria are present in the cytoplasm of maternal gametes only (egg). Paternal gametes (sperm) do not have cytoplasmic

mitochondria and plastids. This **inheritance** is known as **uniparental** when extranuclear genes from only one parent contribute organellar DNA to the offspring. Thus, the phenotype of traits linked to genes found in either chloroplasts or mitochondria are determined exclusively by the maternal parent, so their diseases are received from the mother to their offspring during sexual reproduction. Progeny of an affected female will all show the disease, but if an affected male is crossed to a normal female, all the progeny will be normal.



Cytoplasmic inheritance plays a role in several disease processes:

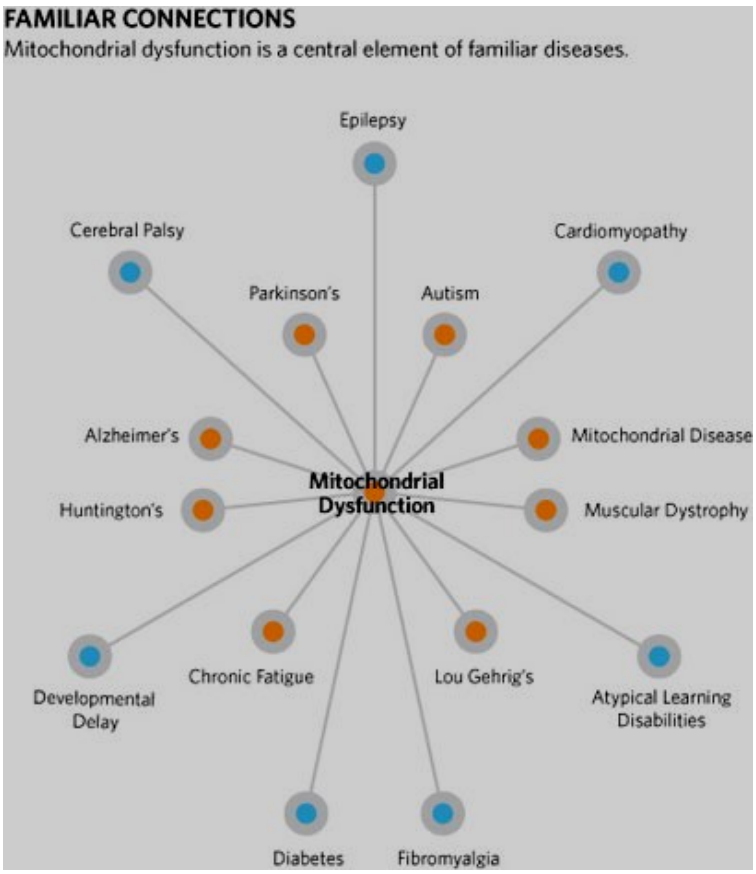
1. Mitochondrial Diseases

One cell contains numerous mitochondria, and each mitochondrion contains dozens of copies of the mitochondrial genome. Moreover, the mitochondrial genome has a higher mutation rate (about 100-fold higher) than the nuclear genome. This leads to a heterogeneous population of mitochondrial DNA within

the same cell, and even within the same mitochondrion; as a result, mitochondria are considered heteroplasmic. When a cell divides, its mitochondria are partitioned between the two daughter cells. However, the process of mitochondrial segregation occurs in a random manner and is much less organized than the highly accurate process of nuclear chromosome segregation during mitosis. As a result, daughter cells receive similar, but not identical, copies of their mitochondrial DNA.

So, we can say that mitochondrial disease refers to any illness resulting from mutation of any genes on mt DNA, which is involved in energy metabolism.

In humans, mutations in mtDNA causes malfunctions in mitochondria lead to multi-systemic defects in the brain, heart, muscles, kidney and endocrine and respiratory systems. The many possible clinical symptoms and diseases include loss of motor control, muscle weakness, heart disease and strock, diabetes (type 2), respiratory problems, Alzheimer's and Parkinson's disease, vision and hearing problems, different types of cancers and developmental delays.



In plants, cytoplasmic male sterility (CMS) in maize (in Texas USA, 1970) arises spontaneously via mutations in nuclear and/or mt genes causing the failure of plants to produce functional anthers, pollen, or male gametes (i.e fertility loss of flowers).

2. Plastids Diseases

The **plastid** is a major organelle found in the cells of plants and algae. Plastids often contain pigments used in photosynthesis. They are the site of manufacture and storage of important chemical compounds (as sugar and starch) used by the cell for producing energy and as raw material for the synthesis of other molecules (amino acids, fatty acids, and diverse isoprenoids).

In plant, Mutant genes that disrupt aspects of chloroplast function can result in abnormal growth, male sterility of flowers, and abnormal photosynthesis.

Examples:

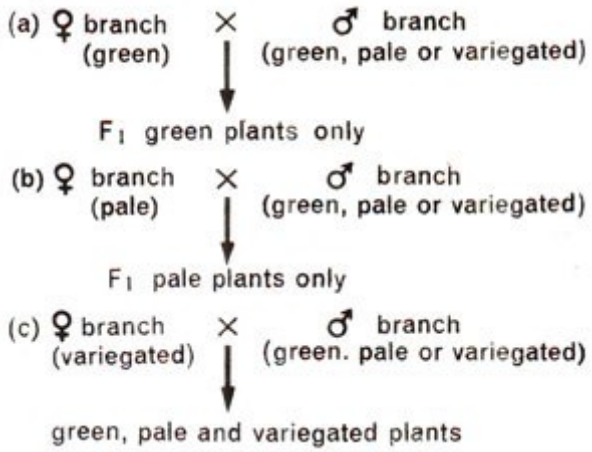
a) Reduced rates of chlorophyll synthesis cause the **chlorophyll loss in leaves and the delay of fruit ripening** (eg strawberry, tomato,..).

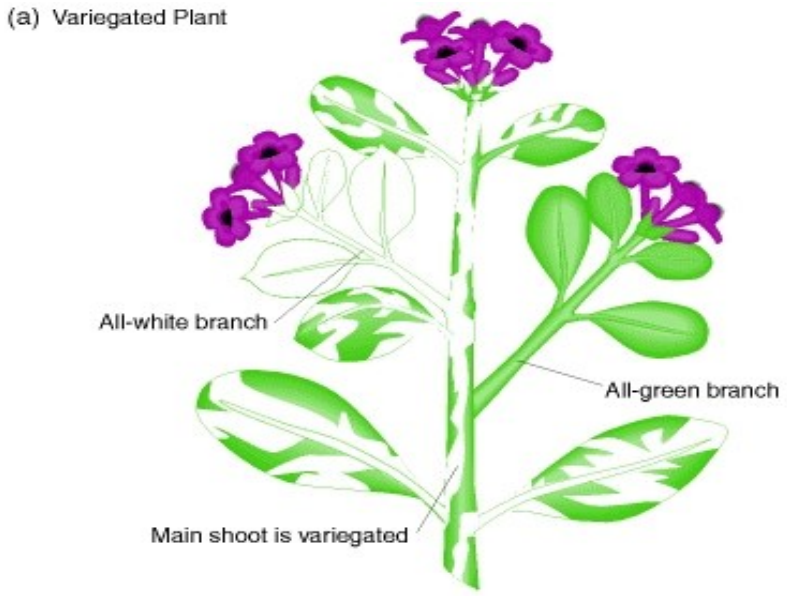
b) Variegation (patched) in *Mirabilis jalapa*

It is believed that variation in color of leaves, branches or whole plants (*Mirabilis* and maize) is due to two kinds of plastids (normal and mutant albino). Three kinds of branches according to occurrence of plastids may be

found: (i) completely green, (ii) completely pale green or (iii) variegated (as patches). In such cases, phenotype of offspring will depend upon phenotype of branch on which flowers are pollinated i.e. depend on the plastids of the egg.

These two types of plastids will faithfully multiply due to cell division, but may not equally distribute themselves to daughter cells. An egg having both kinds of plastids may give rise to three types of offspring namely (i) those with mainly normal green plastids; (ii) those with mainly mutant albino plastids and (iii) those with both kinds of plastids.





(b) Results of crosses between branches

Egg cell of female *(n)*	Pollen cell of male *(n)*	Zygote constitution *(2n)*
White ♀	Any ♂	White
Green ♀	Any ♂	Green
Variegated ♀	Any ♂	
Egg type 1		White
Egg type 2		Green
Egg type 3		Cell division → Variegated

V. Environmental influences on gene expression

(Gene expression–environment interaction or G×E)

The phenotype of an individual is not only the result of inheriting a particular set of parental genes but from the interactions between genes and the environment.

Phenotype = Genotype + Environment

The phenotypes differ in their degree of dependence on environment:

1. Some may **never** be affected
2. Others may be **completely** affected
3. Most of them are **temporary** affected (influenced)

Some environment factors (external and internal) that may **affect** the gene expression (phenotypic appearance):

I. By inducing a phenotype that matches a phenotype of known genotype in the organism **(Phenocopies).**

Eg (1): The Vanessa (butterfly) genus of butterflies have spectrum of phenotypic plasticity to appear similar to the genetical one as they can change the phenotype of their wing color patterns based on the local temperature. A long-term low-temperature treatment or heat-shock treatment produced various modification types, characterized by the expanded or reduced black spots on the proximal forewing, the reduced white band on the dorsal forewing, and unique hindwing patterns.

Eg (2): In Himalayan rabbits. When raised in moderate temperatures, Himalayan rabbits are white in colour with black tail, nose, and ears, making them phenotypically distinguishable from genetically Black rabbits. However, when raised in cold temperatures, Himalayan rabbits show black colouration of their coats, resembling the genetically black rabbits. Hence this Himalayan rabbit is a phenocopy of the genetically black rabbit.

II. By inducing a different phenotype that doesn't match the original phenotype of known genotype in the organism.

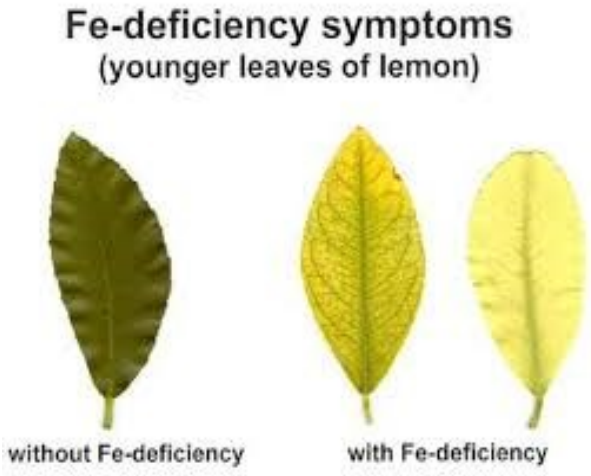
1. Light/Dark

Eg: Albinism in seedlings and plants growing in dark. Plants are green because they contain chloroplasts with chlorophyll that absorbs blue and red

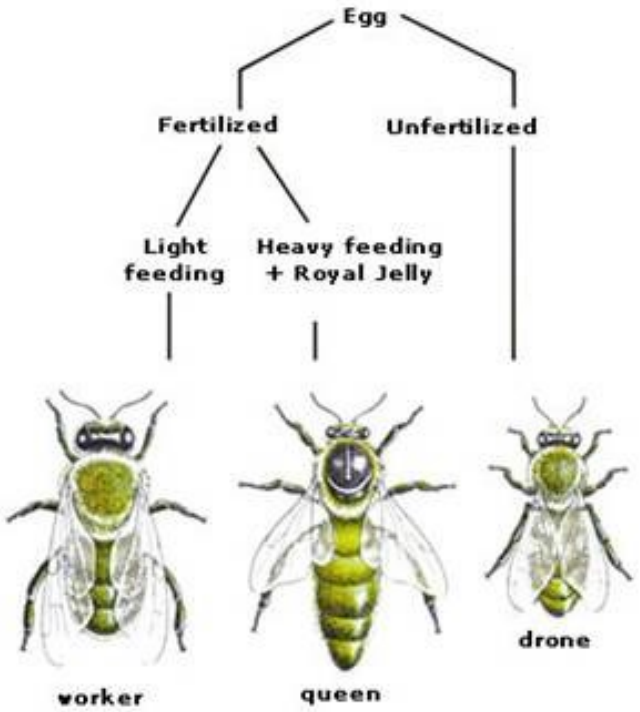
light and reflects light in the green wavelength; that is why it looks green. Therefore, absence of light affects the concentration of chlorophyll in the leaf, in turn, affect gene expression of the color of that leaf.

2. Nutrition

Eg (1): Chlorosis (yellow color) in plants grown in iron lacking soil (Fe-deficiency). Iron Fe is most important for the respiration and photosynthesis processes. Iron is also implied in many enzymatic systems like chlorophyll synthesis. So, its deficiency causes chlorotic yellow of blade but the veins remaining green. At severe deficiency, the leaves may become very pale yellow, and the veins become chlorotic, too.



Eg (2): Quality and quantity of food where determine whether the diploid larvae (fertilized) of **honey bees** may be a female worker or a fertile queen.



3. Temperature

Eg (1): In the **Chinese primrose**, the color of the flowers varies from white, at a temperature of 30°C or over and to pink, at 10-20°C.

Eg(2): The white borderon the wings of mourning **cloak butterflies** that develop in summer, at high temperatures, is sharply delineated; when members of the same species develop in spring, at low temperatures, the outline of the border is diffuse.

Eg (3): After mating at sea, adult female **sea turtles** return to land to nest at night. After the hole is dug, the female then starts filling the nest around 50 to 200 eggs, depending on the species. After laying, she re-fills the nest with sand, then returns to the ocean, leaving the eggs untended. The hatchling's gender depends on the sand temperature: higher temperatures (30°C) results in more female hatchlings, but lower temperature (10-20°C) results male hatchlings.

4. Humidity (or Rain)

The body color of ***Drosophila*** is mainly either black or white, but in humid conditions, the body became striped.

Eg Skeleton flower

The *Diphylleia grayi* is a beautiful white flower that turns transparent upon contact with water. When it rains, the clusters of lovely blooms magically transform into glistening, crystal-like blossoms. Because of this amazing phenomenon, the *Diphylleia grayi* is commonly known as the 'skeleton flower'. The plant generally grows on moist, wooded mountainsides in the colder regions of Japan and China. It is recognizable by its large, umbrella-shaped leaves that are topped with small clusters of pearly white flowers. While the plant is perennial, and can grow up to a height of 0.4 meters, the flowers bloom from mid-spring to early-summer in shady conditions. As the petals of these flowers are soaked in water, they slowly begin to lose their white pigmentation, turning completely transparent over time. When dry, they return to their original white version.

Another skeleton flower is that of a White Lady (*Thunbergia fragrans*) grow in windward moderately wet coastal areas in Hawaii.

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Students assignment: Compare between leucism and Albinism?