EXTENSION OF MENDELIAN INHERITANCE: BEYOND MENDELIAN GENETICS (part 2)

III. 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.

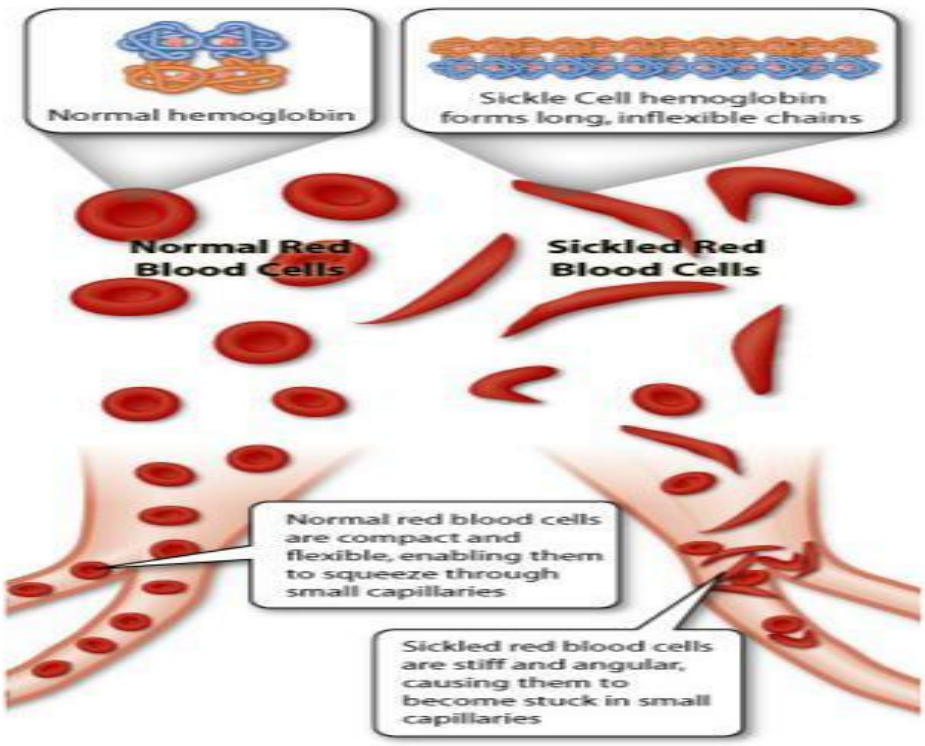
Eg (1): Sickle-cell anemia

The **mutant gene causing abnormal Hb^{s} hemoglobin** of $Hb^{S}Hb^{S}$ 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.

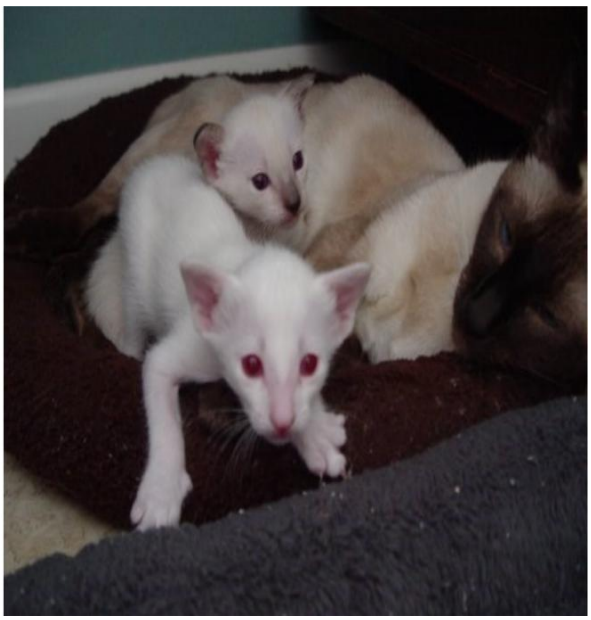
ii. Severe anemia known as sickle-cell anemia

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

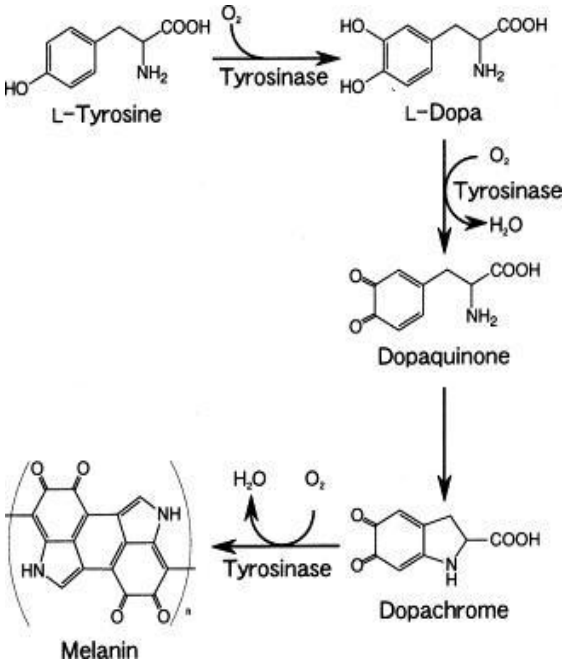


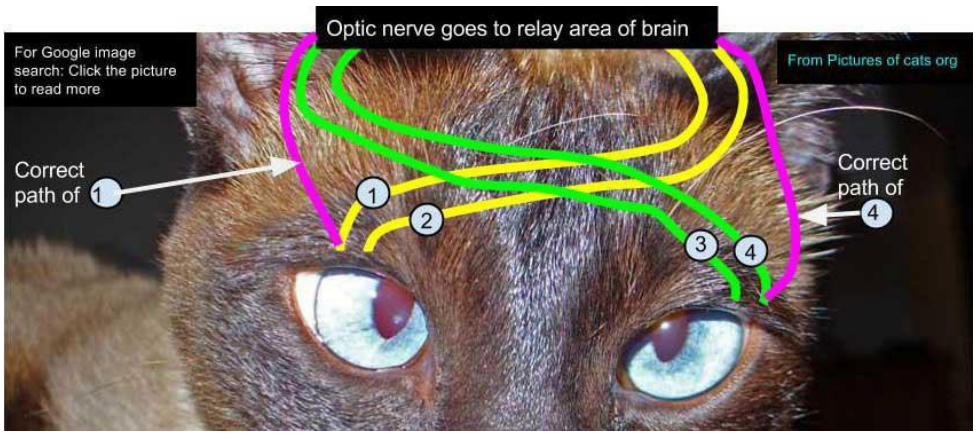
Eg (2): the coloration pattern and crossed eyes of Siamese cats

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, but also exhibit incorrect projections from retina to brain, 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).





Eg (3): Coloration pattern and deafness in Dalmatian

Dalmatian puppies are born with both albinism and deafness caused by the absence of pigment producing cells (melanocytes) in the inner ear. Their first spots usually appear within 3 to 4 weeks after birth. After about a month, they have most of their spots, although they continue to develop throughout life at a much slower rate. The Blue-eyed Dalmatians are thought to have a greater incidence of deafness than brown-eyed Dalmatians. Deafness can be unilateral (affecting one ear) or bilateral (affecting both ears) according to the place of melanin formation.

Eg (4): Albinism in animals

An Albino is an absence of colour. It is generally homozygous recessive "aa" with white skin and hair across the whole body (pigment free), or just part of the body, and pink eye pupils. It is a pigmentless "white" phenotype determined by a mutation (absence or defect) in a gene coding for melanin synthesizing enzyme (tyrosinase) in either the somatic tissue or the germinal tissue, resulting the body's inability to make melanin. Albinism is a rare condition usually inherited in an autosomal recessive Mendelian pattern in many animals. The pink or red eye pupils is due to the lack of melanin production in both the retinal pigmented epithelium (RPE) and iris, caused by the unmasking of the red hemoglobin pigment in the blood vessels of the retina.

Eg (5): Leucism of animals

Leucism is defects in multiple types of pigment (not just melanin) cell differentiation and/or migration from the neural crest to skin, hair, or feathers during development forming white, pale, or patchy coloration of the skin, hair, feathers, scales or cuticle of animals in either the entire surface (if all pigment cells fail to develop) or patches of body surface (if only a subset are defective). Most leucistic animals have normally coloured eyes (black) because the melanocytes of the retinal pigmented epithelium (RPE) are not derived from the neural crest, instead an outpouching of the neural tube generates the optic cup which, in turn, forms the retina. As these cells are from an independent developmental origin, they are typically unaffected by the genetic cause of leucism.

Leucism lion

Albino lion

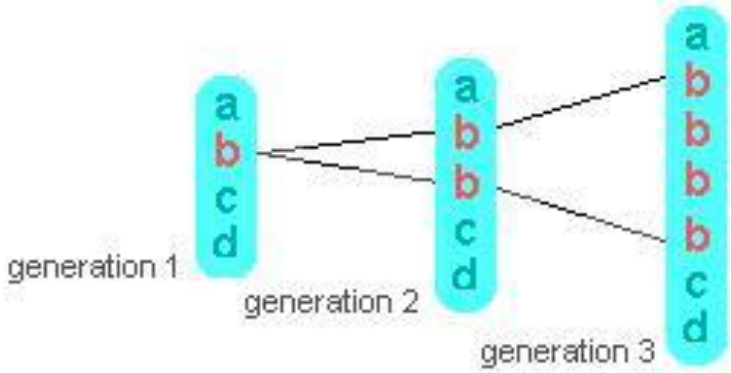
NOTE:

The pigmentation is given by melanocytes, specialized cells that produce and contain melanin. Melanocytes are formed during embryonic development in a part of the embryo defined as the neural crest. In addition to these cells, the neural crest gives birth to various organs. During development, melanocytes migrate to the epidermis, hair follicles, but to the eye, inner ear and other organs.

A stable and heritable (able to be inherited) modification of the sequence of nucleotides in the genetic code is known as mutation. In a mutation, not all melanocytes grow and migrate properly. They will also not produce melanin and white spots are observed. These can be more or less extensive but are nothing more than hairs devoid of pigment.

2. Stuttering Alleles

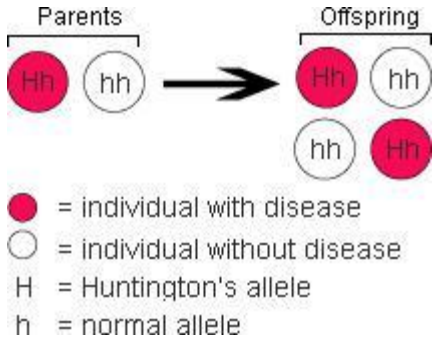
Mendel believed that all units of inheritance are passed on to offspring unchanged **but stuttering alleles or unstable alleles** are an important exception to this rule. Some genetically inherited diseases have more severe symptoms by each succeeding generation due to segments of the defective genes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



Eg Huntington's disease,

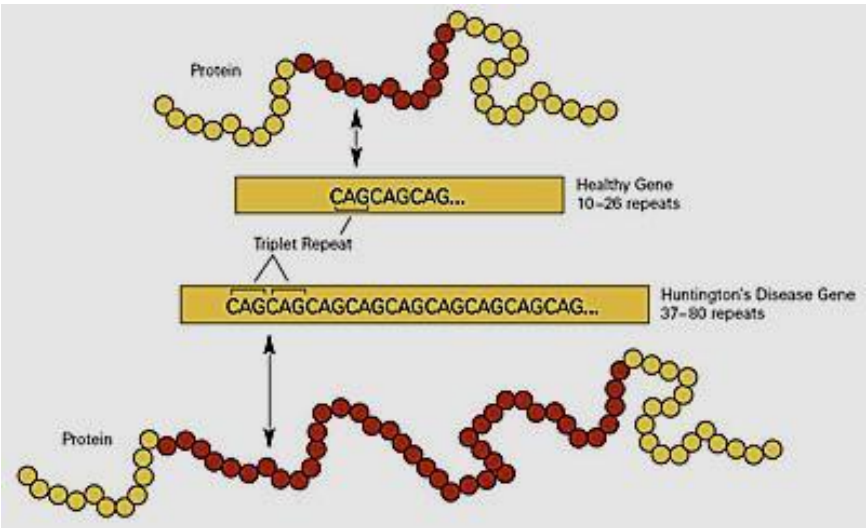
Eg: Huntington's disease

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.



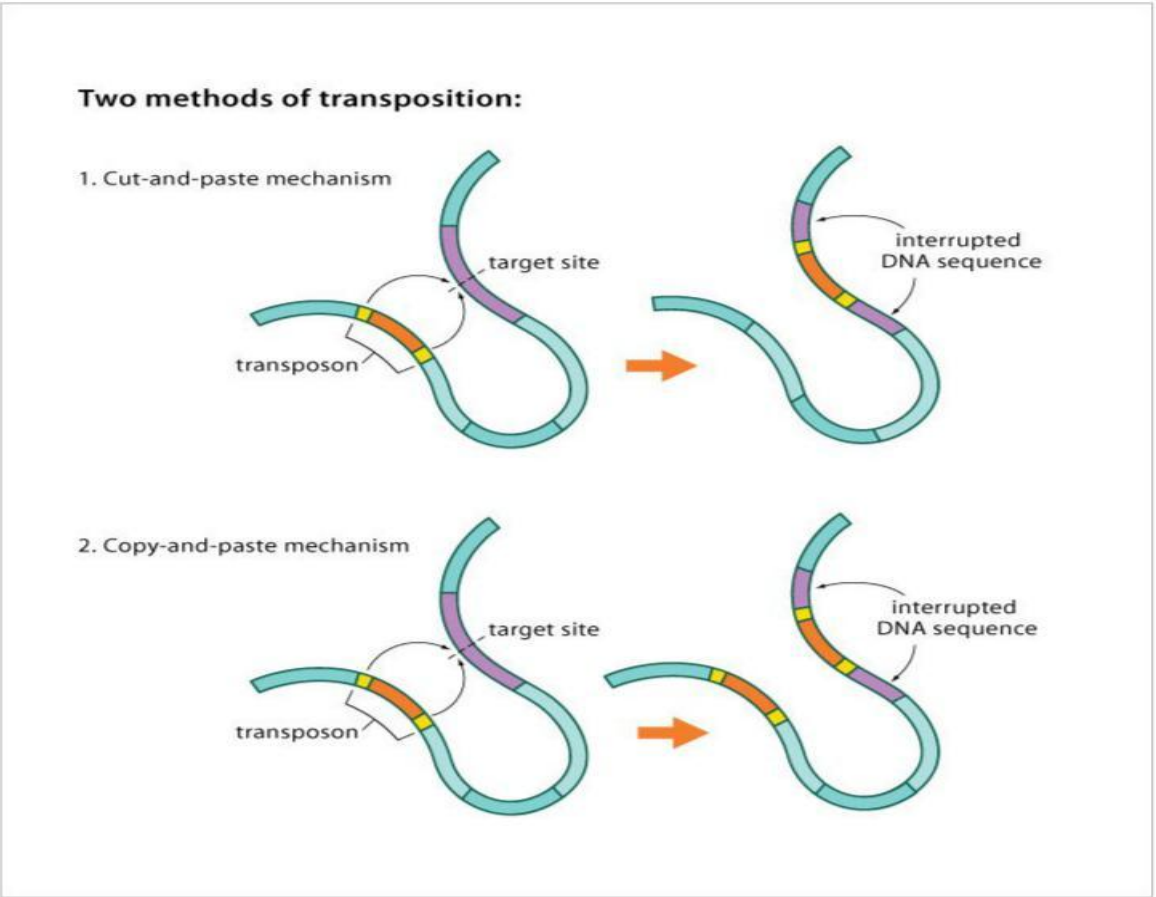
Part of this gene is a repeated section called a trinucleotide repeat, which varies in length between individuals and may change length between generations.

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.



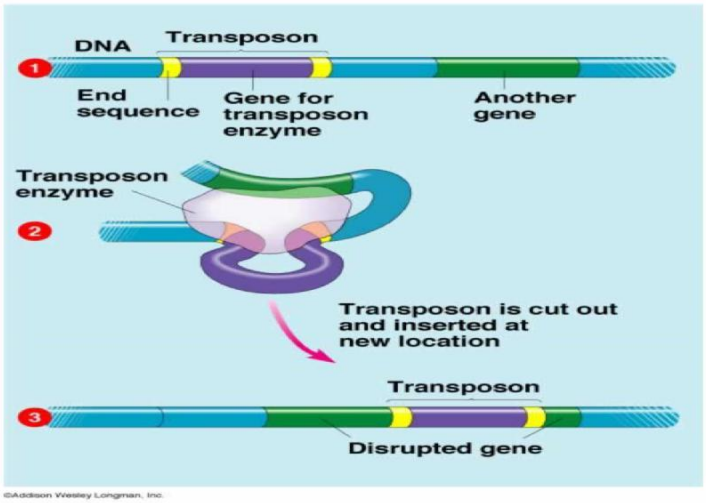
1. Transposons (Jumping genes)

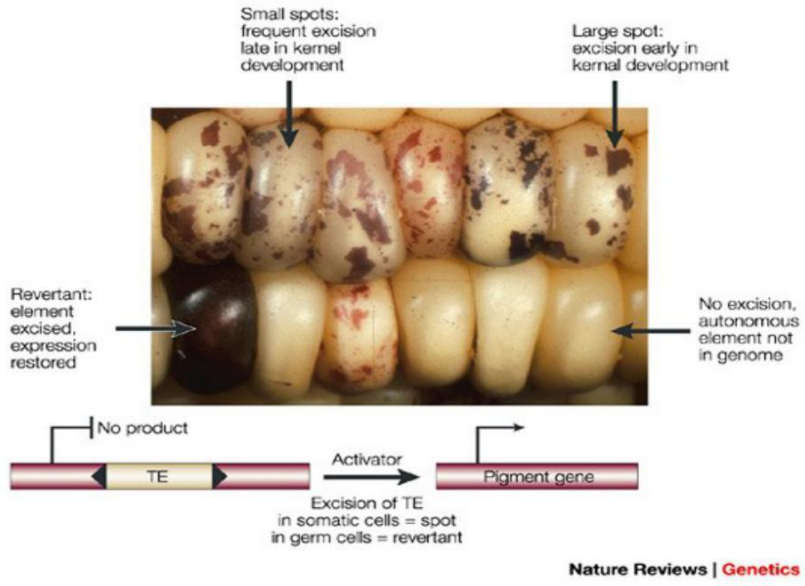
Eg Grains of Indian corn comes in different colors, such as purple, yellow and white. Sometimes the individual grains are purple with white streaks or mottling. This mottling effect defies Mendel's basic principles of genetics because individual grains may be multicolored rather than a single color. 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.

IV. Polygenic inheritance: gene interaction.

Epistasis is the phenomenon of the effect of one gene being dependent on the presence of one or more 'modifier genes', the genetic background. Thus, epistatic have different effects in combination than individually as alleles of one gene pair (**epistatic**) can influence, cover up (mask), or alter the expression of alleles of another gene pair (**hypostatic**). It was originally a concept from genetics but is now used in biochemistry, computational biology and evolutionary biology. It arises due to interactions, either between genes, or within them, leading to non-additive effects.

The classical cross between 2 heterozygous give the following genotypes:

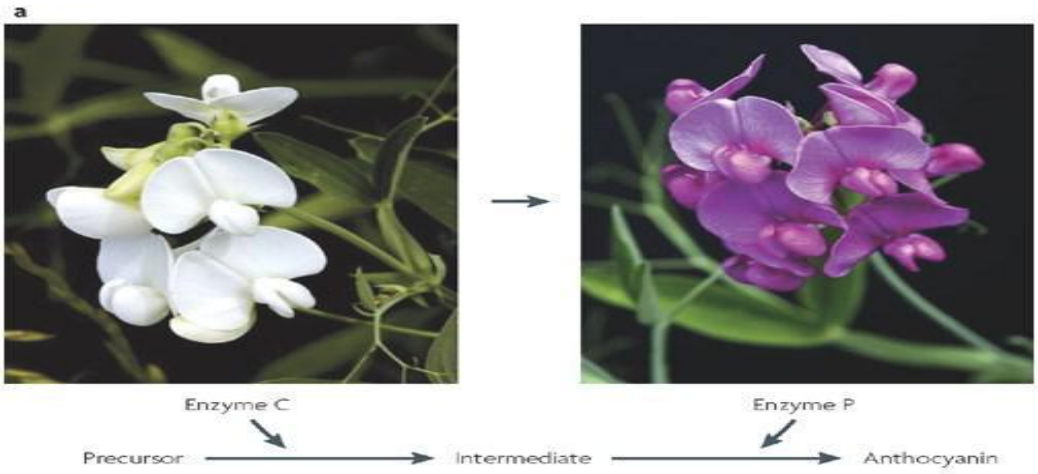
A-B- : A-bb : aaB- : aabb (4 different phenotypes)

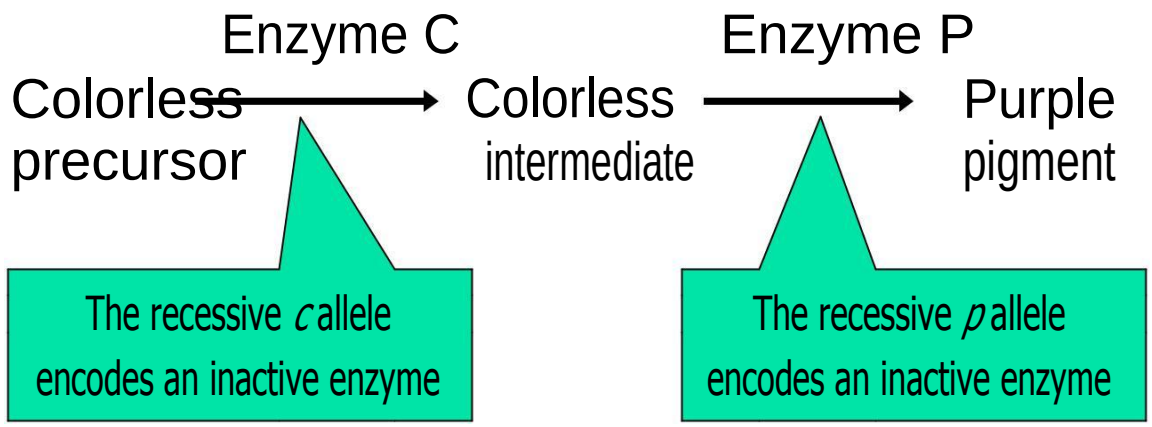
9 3 3 1

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 <u>modify</u> the above ratio or <u>produce</u> 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.

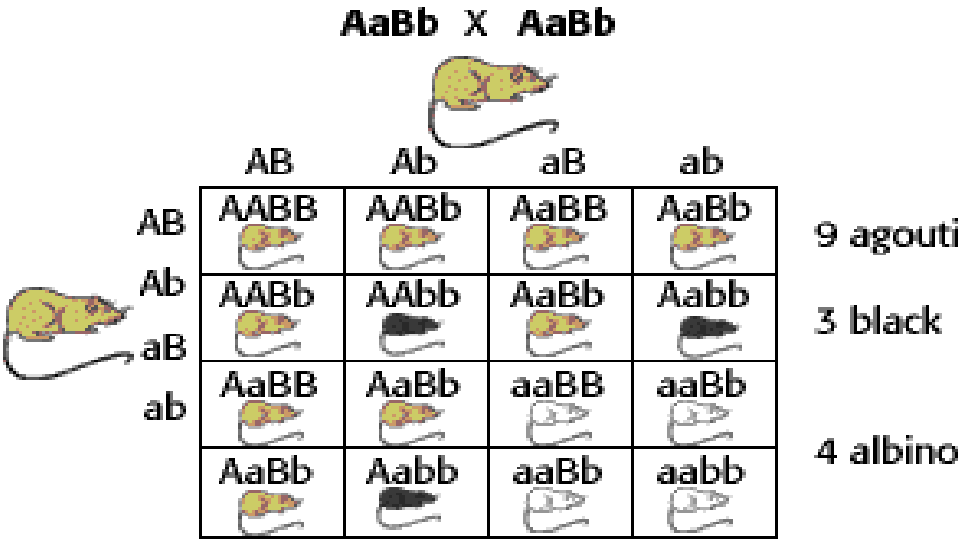
Genes reveal different epistatic relations:

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 (1): Skin color of house mouse

Crossing AABB x aabb or AAbb x aaBB will have F_1 AaBb and by crossing AaBb x AaBb, 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)

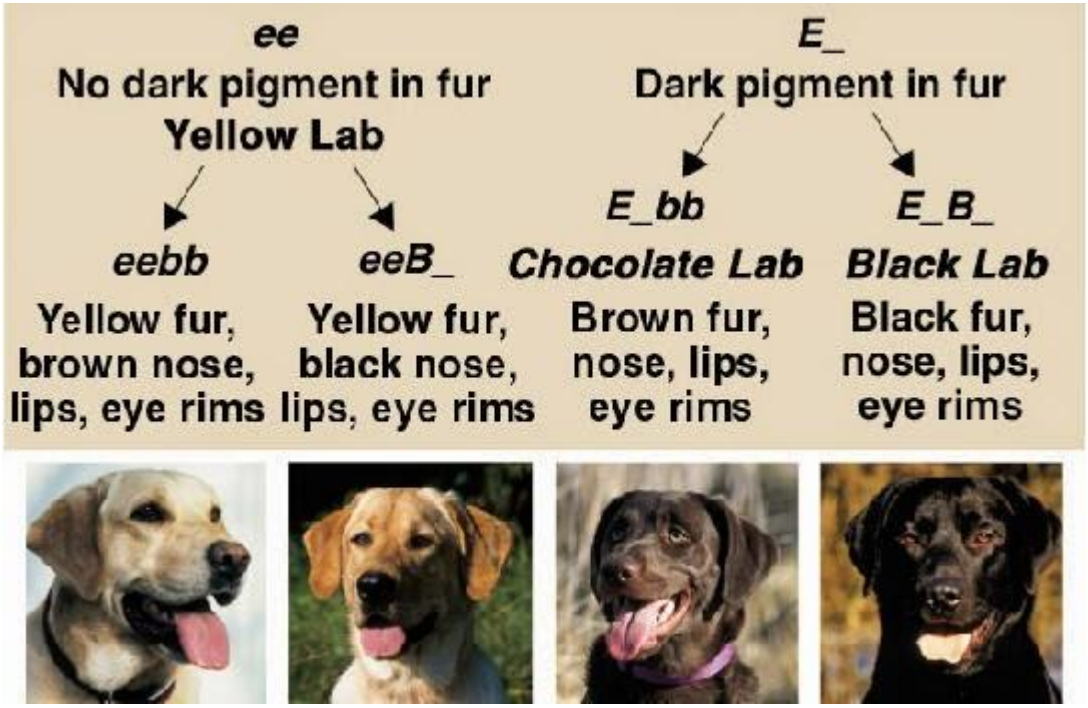
9 3 (3 + 1)

9 3 4

Eg (2): coat color of Labrador dogs

Crossing EeBb x EeBb, the offspring will have a ratio 9:3:4

	EB	Eb	eB	eb
EB	EEBB	EEBb	EeBB	EeBb
Eb	EEBb	EEbb	EeBb	Eebb
eB	EeBB	EeBb	eeBB	eeBb
eb	EeBb	Eebb	eeBb	eebb



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.

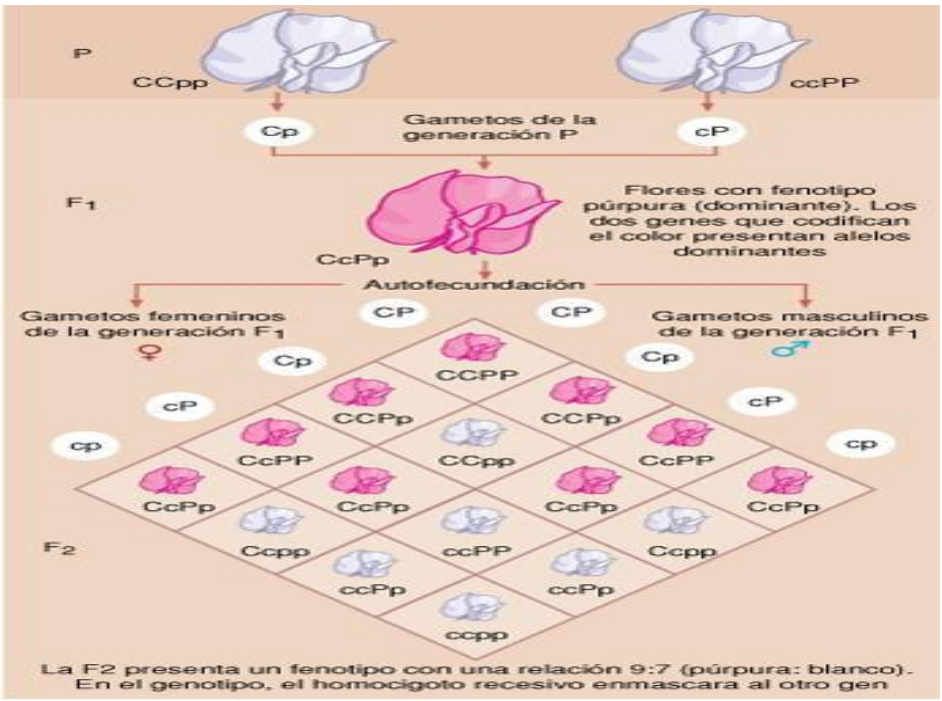
Eg: Flower color of sweet pea (*Lathyrus*)

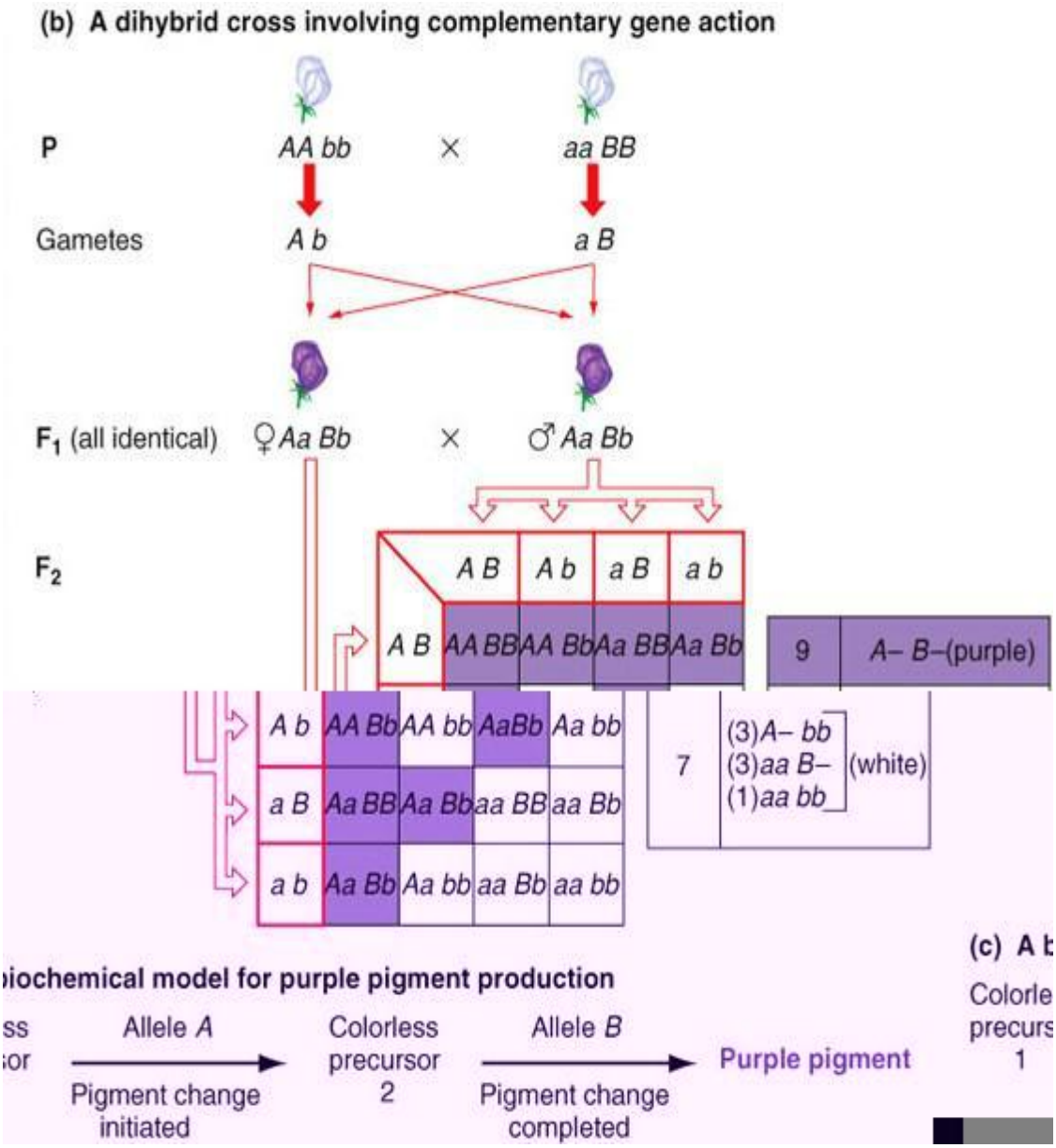
Crossing AABB x aabb or AAbb x aaBB will have F_1 AaBb and F_2 will have a ratio 9:7, where A=Pink, B=Pink, aa or bb=white.

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
F1 (all identical)
♀Aa Bb
×
♂Aa Bb
F2
A B
A b
a B
a b
A B
AA BB
AA Bb
Aa BB
Aa Bb
9
A– B–(purple)
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
7
(3)A– bb
(3)aa B–
(1)aa bb
(white)
(c) A b
iochemical model for purple pigment production
ss
or
Allele A
Pigment change initiated
Colorless precursor 2
Allele B
Pigment change completed
Purple pigment
Colorle
precurs
1

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.

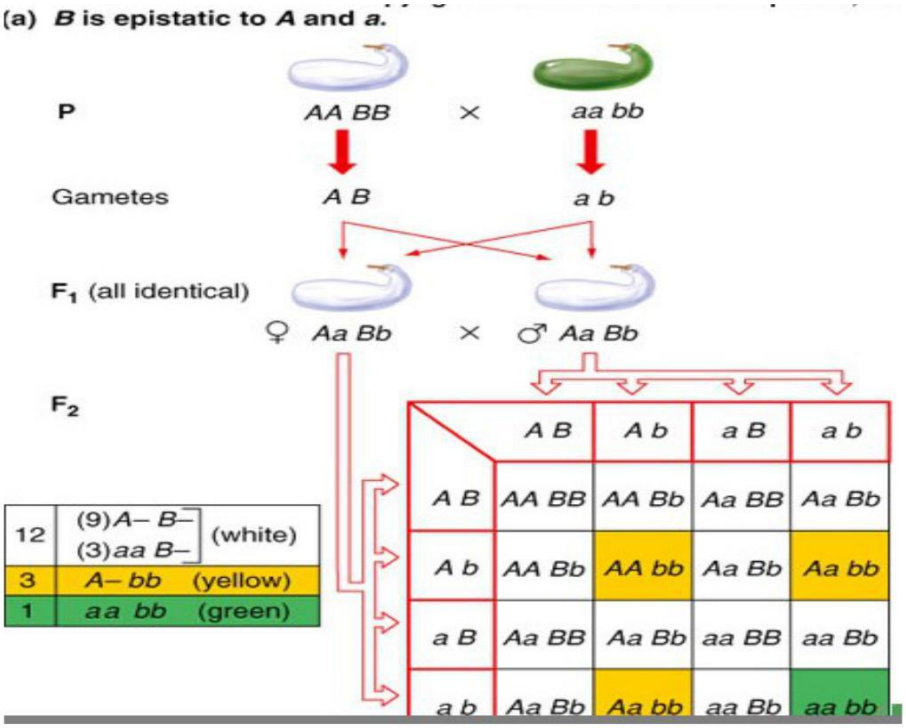
Eg: Fruit color of *Cucurbita*

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.

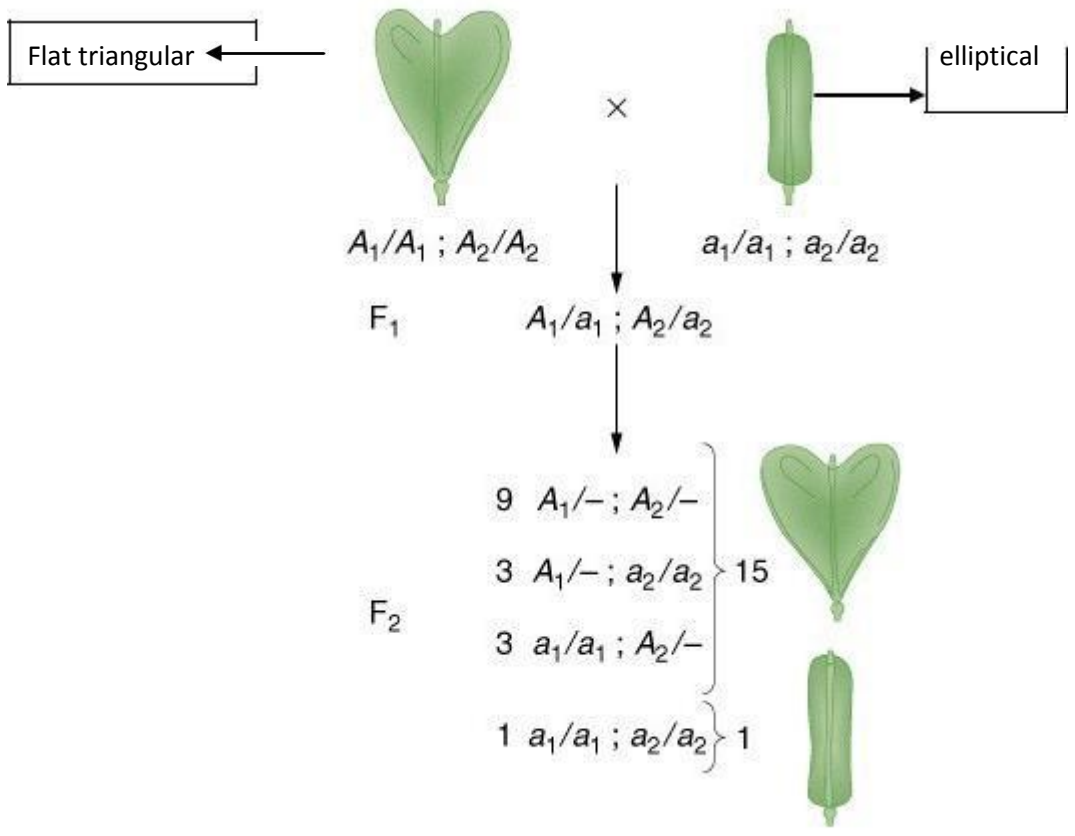
Eg: Fruit shape of *Capsella*

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**.

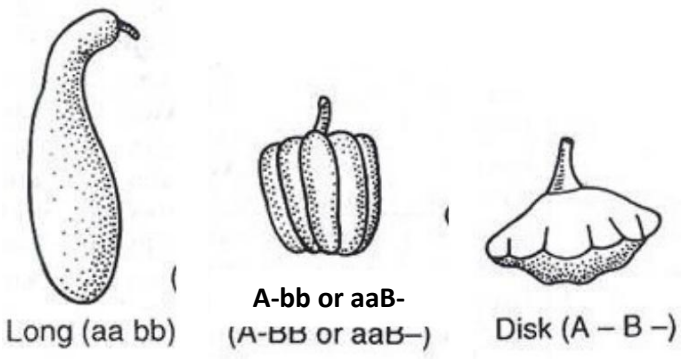
6. Duplicate genes with cumulative effect (9:6:1)

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?

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