FIFTH SEM GENERAL

UNIT 2 GENETICS

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1. LINKAGE : ITS MECHANISMS AND SIGNIFICANCE

When two or more characters of parents are transmitted to the offsprings of few generations such as F1, F2, F3 etc. without any recombination, they are called as the linked characters and the phenomenon is called as linkage.

This is a deviation from the Mendelian principle of independent assortment.

Mendel's law of independent assortment is applicable to the genes that are situated in separate chromosomes. When genes for different characters are located in the same chromosome, they are tied to one another and are said to be linked.

They are inherited together by the offspring and will not be assorted independently. Thus, the tendency of two or more genes of the same chromosome to remain together in the process of inheritance is called linkage.

Bateson and Punnet (1906), while working with sweet pea (Lathyrus odoratus) observed that flower colour and pollen shape tend to remain together and do not assort independently as per Mendel's law of independent assortment.

When two different varieties of sweet pea—one having red flowers and round pollen grain and other having blue flower and long pollen grain were crossed, the F1 plants were blue flowered with long pollen (blue long characters were respectively dominant over red and round characters). When these blue long (heterozygous) hybrids were crossed with double recessive red and round (homozygous) individuals (test cross), they failed to produce expected 1:1:1:1 ratio in F2 generation. These actually produced following four combinations in the ratio of 7 : 1 : 1 : 7 (7 blue long : 1 blue round : 1 red long : 7 red round) (Fig. 5.6).

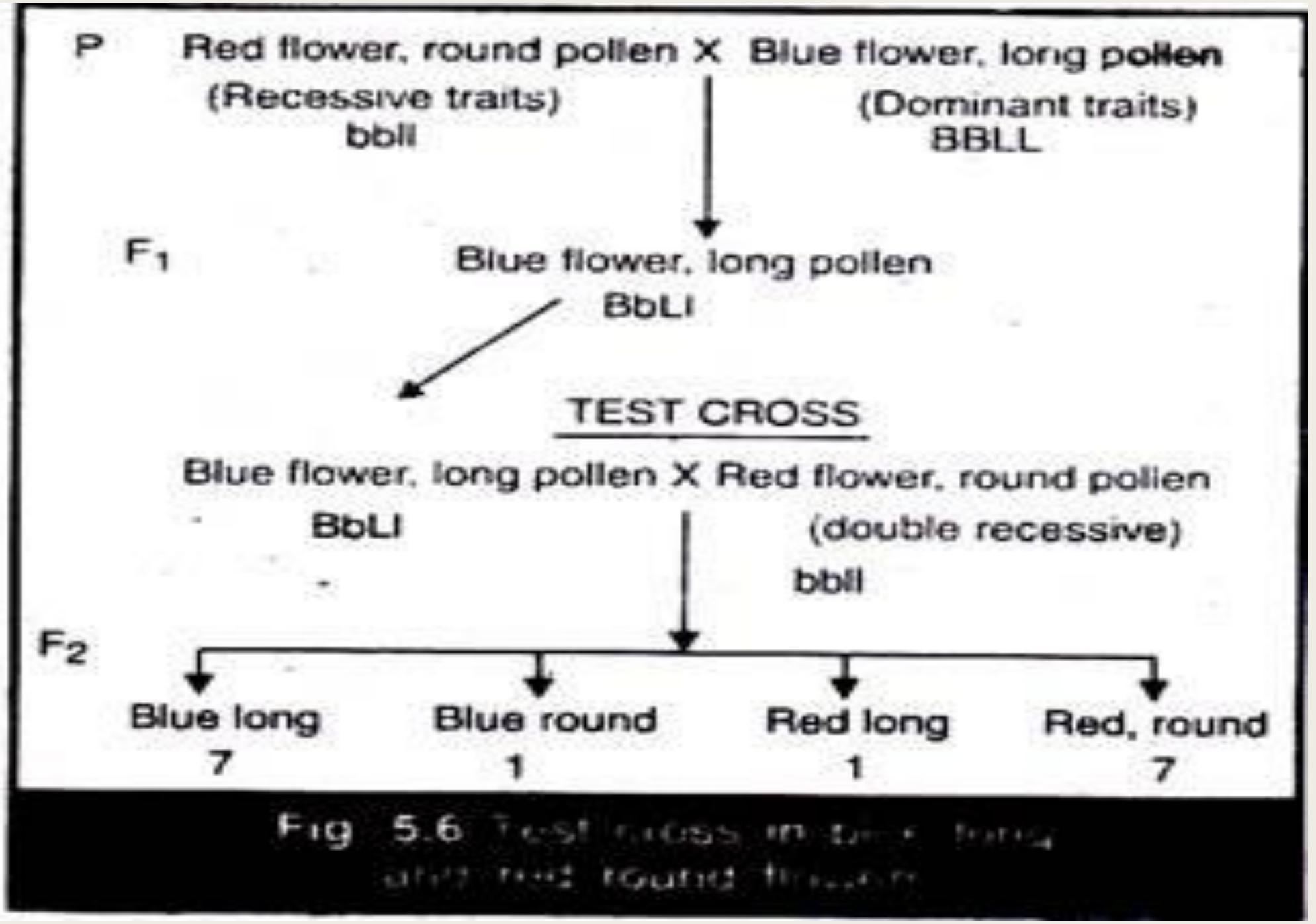

Fig 5.6 Test cross in [illegible]

The above result of the test cross clearly indicates that the parental combinations (blue, long and red, round) are seven times more numerous than the non-parental combinations. Bateson and Punnet suggested that the genes (such as B and L) coming from the same parent (BBLL × bbll) tend to enter the same gamete and to be inherited together (coupling). Similarly, the genes (B and 1) coming from two different parents (such as BBLL x bbll), tend to enter different gametes and to be inherited separately and independently (repulsion).

Morgan's View of Linkage:

Morgan (1910), while working on Drosophila stated that coupling and repulsion are two aspects of linkage. He defined linkage as the tendency of genes, present in the same chromosome, to remain in their original combination and to enter together in the same gamete.'

The genes located on the same chromosome and are being inherited together are known as linked genes, and the characters controlled by these are known as linked characters.

Their recombination frequency is always less than 50%. All those genes which are located in the single chromosome form one linkage group. The total number of linkage group in an organism corresponds to the number of chromosome pairs. For example, there are 23 linkage groups in man, 7 in sweet pea and 4 in Drosophila melanogaster.

Features of Theory of Linkage:

Morgan and Castle formulated 'The Chromosome Theory of Linkage'.

It has the following salient features:

1. Genes that show linkage are situated in the same chromosome.

2. Genes are arranged in a linear fashion in the chromosome i.e., linkage of genes is linear.

3. The distance between the linked genes is inversely proportional to the strength of linkage. The genes which are closely located show strong linkage, whereas those, which are widely separated, have more chance to get separated by crossing over (weak linkage).

4. Linked genes remain in their original combination during course of inheritance.

5.. The linked genes show two types of arrangement on the chromosome. If the dominant alleles of two or more pairs of linked genes are present on one chromosome and their recessive alleles of all of them on the other homologue (AB/ab), this arrangement is known as cis-arrangement. However, if the dominant allele of one pair and recessive allele of second pair are present on one chromosome and recessive and dominant alleles on the other chromosome of a homologous pair (Ab/aB), this arrangement is called trans arrangement (Fig. 5.7).

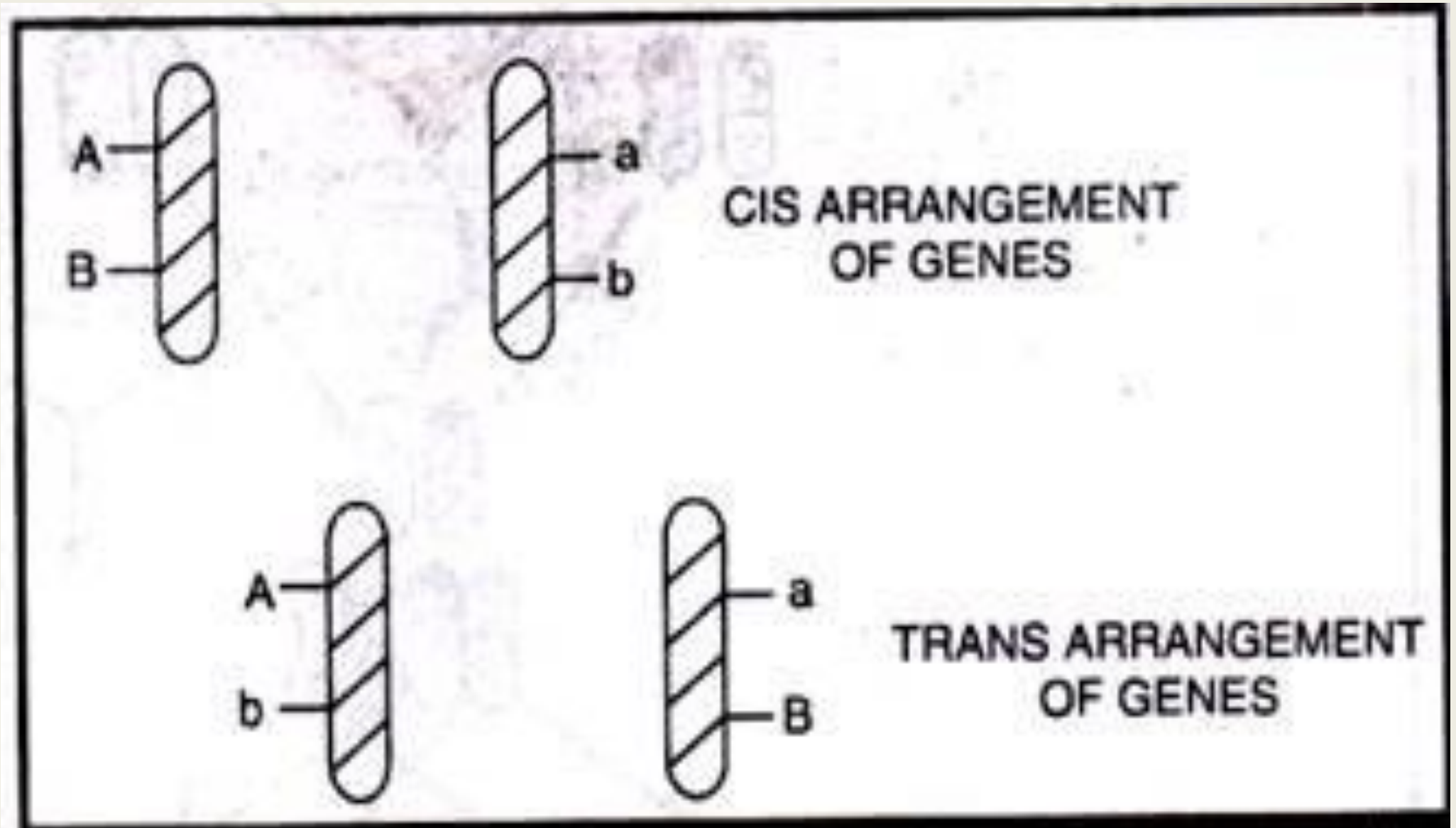

Fig. 5.7 Diagram showing cis and trans arrangement of linked genes.

Examples of Linkage:In MAIZE:

Maize provides a good example of linkage. Hutchinson crossed a variety of maize having coloured and full seed (CCSS) with a variety having colourless and shrunken seeds (ccss). The gene C for colour is dominant over its colourless allele c and the gene S for full seed is dominant over its shrunken allele s. All the F1 plants produced coloured and full seed. But in a test cross, when such F1 females (heterozygous) are cross pollinated with the pollen from a plant having colourless and shrunken seeds (double recessive), four types of seeds are produced (Fig. 5.8).

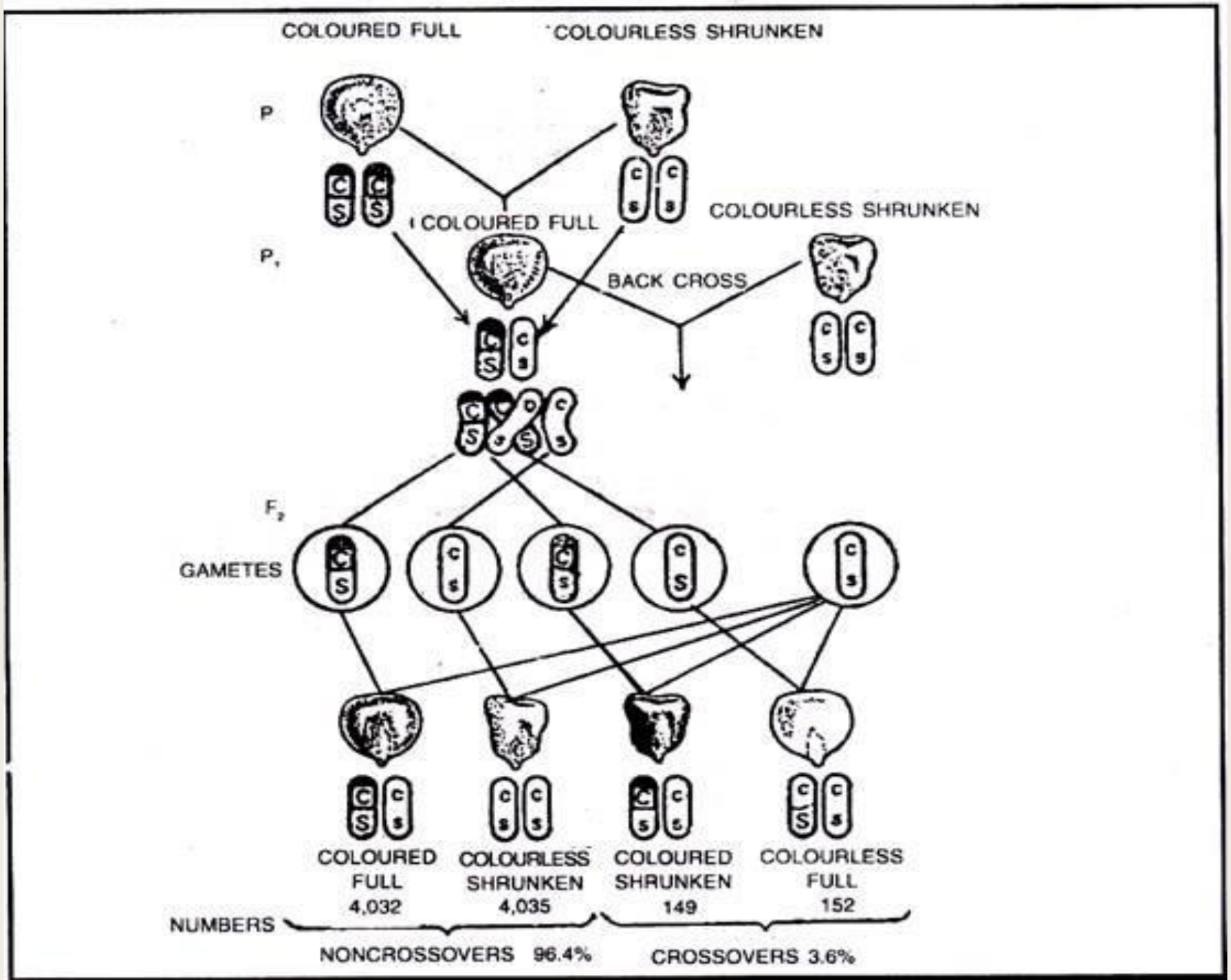

Fig. 5.8 Chromosomal interpretation of linkage and crossing over in maize.

These are:

(*i*) Coloured full (CS)	- 4,032/8368	Parental combination = 96.4%
(*ii*) Colourless shrunken (cs)	- 4,035/8368	
(*iii*) Coloured shrunken (Cs)	- 149/8368	New combination
(*iv*) Colourless full (cS)	- 152/8368	= 3.6%

From the above stated result it is clear that the parental combinations are more numerous (96.4%) than the new combination (3.6%). This clearly indicates that the parental characters are linked together. Their genes are located in the same chromosome and only in 3.6% individuals these genes are separated by crossing over. This is an example of incomplete linkage.

In Drosophila:

Morgan (1911) crossed an ordinary wild type Drosophila with grey body and long wings (BB VV) with another Drosophila (mutant type) with black body and vestigial wings (bbvv). All the hybrids in F_1 generation are with grey bodies and long wings (BbVv) i.e., phenotypically like the wild type of parents. If now a male of F, generation (Bb Vv) is back crossed with a double recessive female (test cross) having black body and vestigial wings (bbvv) only parental combinations are formed in F_2 generation without the appearance of any new combinations. The results indicate that grey body character is inherited together with long wings.

It implies that these genes are linked together. Similarly, black body character is associated with vestigial wing. Since only parental combinations of character appear in the offspring of F2 generation and no new or non-parental combinations appear, this shows complete linkage. Complete linkage is seen in Drosophila males.

Types of Linkage:

Depending upon the presence or absence of new combinations or non-parental combinations, linkage can be of two types

(i) Complete Linkage:

If two or more characters are inherited together and consistently appear in two or more generations in their original or parental combinations, it is called complete linkage. These genes do not produce non-parental combinations.

Genes showing complete linkage are closely located in the same chromosome. Genes for grey body and long wings in male Drosophila show complete linkage.

(ii) Incomplete Linkage:

Incomplete linkage is exhibited by those genes which produce some percentage of non-parental combinations. Such genes are located distantly on the chromosome. It is due to accidental or occasional breakage of chromosomal segments during crossing over.

Significance of Linkage:

(i) Linkage plays an important role in determining the nature of scope of hybridization and selection programmes.

(ii) Linkage reduces the chance of recombination of genes and thus helps to hold parental characteristics together. It thus helps organism to maintain its parental, racial and other characters. For this reason plant and animal breeders find it difficult to combine various characters.

CROSSING OVER ..ITS MECHANISMS TYPES AND SIGNIFICANCE

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Significance of Crossing Over

1. Meaning of Crossing Over:

Crossing over refers to the interchange of parts between non-sister chromatids of homologus chromosomes during meiotic prophase (pachytene). In other words, crossing over results from exchange of genetic material between non-sister chromatids involving breakage and reunion at precise point. The term crossing over was first used by Morgan and Cattell in 1912.

2. Feature of Crossing Over:

The main features of crossing over are given below:

1. Crossing over takes place during meiotic prophase, i.e., during pachytene. Each pair of chromosome has four chromatids at that time.

2. Crossing over occurs between non-sister chromatids. Thus one chromatid from each of the two homologus chromosomes is involved in crossing over.

3. It is universally accepted that crossing over takes place at four strand stage.

4. Each crossing over involves only two of the four chromatids of two homologus chromosomes. However, double or multiple crossing over may involve all four, three or two of the four chromatids, which is very rare.

5. Crossing over leads to re-combinations or new combinations between linked genes. Crossing over generally yields two recombinant types or crossover types and two parental types or non-crossover types.

6. Crossing over generally leads to exchange of equal segments or genes and recombination is always reciprocal. However, unequal crossing over has also been reported.

7. The value of crossover or recombinants may vary from 0-50%.

8. The frequency of recombinants can be worked out from the test cross progeny. It is expressed as the percentage ratio of recombinants to the total population (recombinants + parental types). Thus,

$$\text{Crossing over frequency (\%)} = \frac{\text{No. of recombinants}}{\text{Total progeny}} \times 100$$

Cases of two strand crossing over, somatic crossing over, sister strand crossing over and unequal crossing over are also known. However, frequency of such cases is extremely low, i.e. in fractions. Crossing over differs from linkage in several aspects (Table 9.1).

TABLE 9.1. Differences between crossing over and linkage

Crossing over	*Linkage*
1. It leads to separation of linked genes.	It keeps the genes together.
2. It involves non-sister chromatids of homologous chromosomes.	It involves individual chromosome.
3. Frequency of crossing over can never exceed 50%.	Linkage groups can never be more than haploid chromosome number.
4. It increases variability by forming new gene combinations.	It reduces variability.
5. It provides equal frequency of parental and recombinant types in test cross progeny.	Provides higher frequency of parental types than recombinant types in test cross progeny.

Chiasma and Crossing Over:

The point of exchange of segments between non-sister chromatids of homologous chromosomes during meiotic prophase is called chiasma (pleural chiasmata). It is thought to be the place where crossing over takes place. Chiasma was first discovered by Janssens in 1909. Depending on the position, chiasma is of two types, viz., terminal and interstitial.

When the chiasma is located at the end of the pairing chromatids, it is known as terminal chiasma and when it is located in the middle part of non-sister chromatids, it is referred to as interstitial chiasma. Later on interstitial chiasma is changed to terminal position by the process of chiasmaterminalization.

The number of chiasma per bivalent may vary from one to more than one depending upon the length of chromatids. When two chiasmata are formed, they may involve two, three or all the four chromatids

Chiasma Terminalization:

The movement of chiasma away from the centromere and towards the end of tetrads is called terminalization. The total number of chiasmata terminalized at any given stage or time is known as coefficient of terminalization. Generally, chiasma terminalization occurs between diplotene and metaphase I.

There are three theories to explain the mechanism of chiasma terminalization, viz:

1. Electrostatic hypothesis,

2. Coiling hypothesis, and

3. Elastic chromosome repulsion theory.

i. Electrostatic Hypothesis:

According to this hypothesis, terminalization takes place due to localized repulsion force in centromere and generalized repulsion force on chromosome surface during diplotene stage.

ii. Coiling Hypothesis:

According to this hypothesis, terminalization takes place by mechanical tension developed within the chromosome due to coils. Thus tension force becomes greater than the force binding the chromatids at the point of exchange resulting in terminalization.

iii. Elastic Chromosome Repulsion:

According to this theory, all bodies having a definite shape resist any change that leads to alter their shapes. Chiasma forces the chromosome out of shape by its binding force. This leads to the development of repulsion at the point of exchange resulting in terminalization of chiasma.

3. Relationship between Crossing Over and Chiasma Formation:

There are two main theories to explain the relationship between crossing over and chiasma formation, viz., 1. classical theory and 2. chiasma type theory.

These are briefly described below:

i. Classical Theory:

This theory states that first chiasma is formed and then crossing over takes place. The genetic crossing over occurs as a result of physical strain imposed by chiasma formation. The chiasma is formed at diplotene stage of meiosis and crossing over occurs between diplotene and anaphase.

In this case, 1 : 1 relationship between chiasmata and crossing over is not observed because chiasma may not lead to breakage and subsequent genetic crossing over.

ii. Chiasma Type Theory:

This theory was proposed by Ianssens and later on elaborated by Belling and Darlington. According to this theory, first crossing over occurs and then chiasma is formed. The crossing over occurs sometimes during early meiotic stages, perhaps at pachytene, when homologous chromatids are closely paired.

As the meiotic cell moves towards metaphase and reductional division, a chiasma is formed at the point where crossing over has occurred.

Thus according to this theory each chiasma represents one genetic cross over.

This theory remains at present the most accepted explanation for the relationship between genetic crossing over and cytological observed chiasmata.

4. Molecular Mechanism of Crossing Over:

There are two important theories viz:

1. Copy choice theory and 2. Breakage and reunion theory to explain the mechanism of crossing over.

These are briefly presented below:

i. Copy Choice Theory:

This theory was proposed by Belling. This theory states that the entire recombinant section or part arises from the newly synthesised section. The non-sister chromatids when come in close contact they copy some section of each other resulting in recombination. According to this theory, physical exchange of preformed chromatids does not take place.

The non-sister chromatids when come together during pairing, copy part of each other. Thus, recombinant chromosome or chromatids have some alleles of one chromatids and some of other. The information may be copied by one strand or both the strands. When only one strand copies, non-reciprocal recombinant is produced. If copy process involves both strands of chromosomes, reciprocal recombinants are produced. Assume, there are two chromosomes, viz., AB and ab. When their chromatids come in close contact they copy each other and result in Ab and aB re-combinations besides parental combinations (Fig. 9.1).

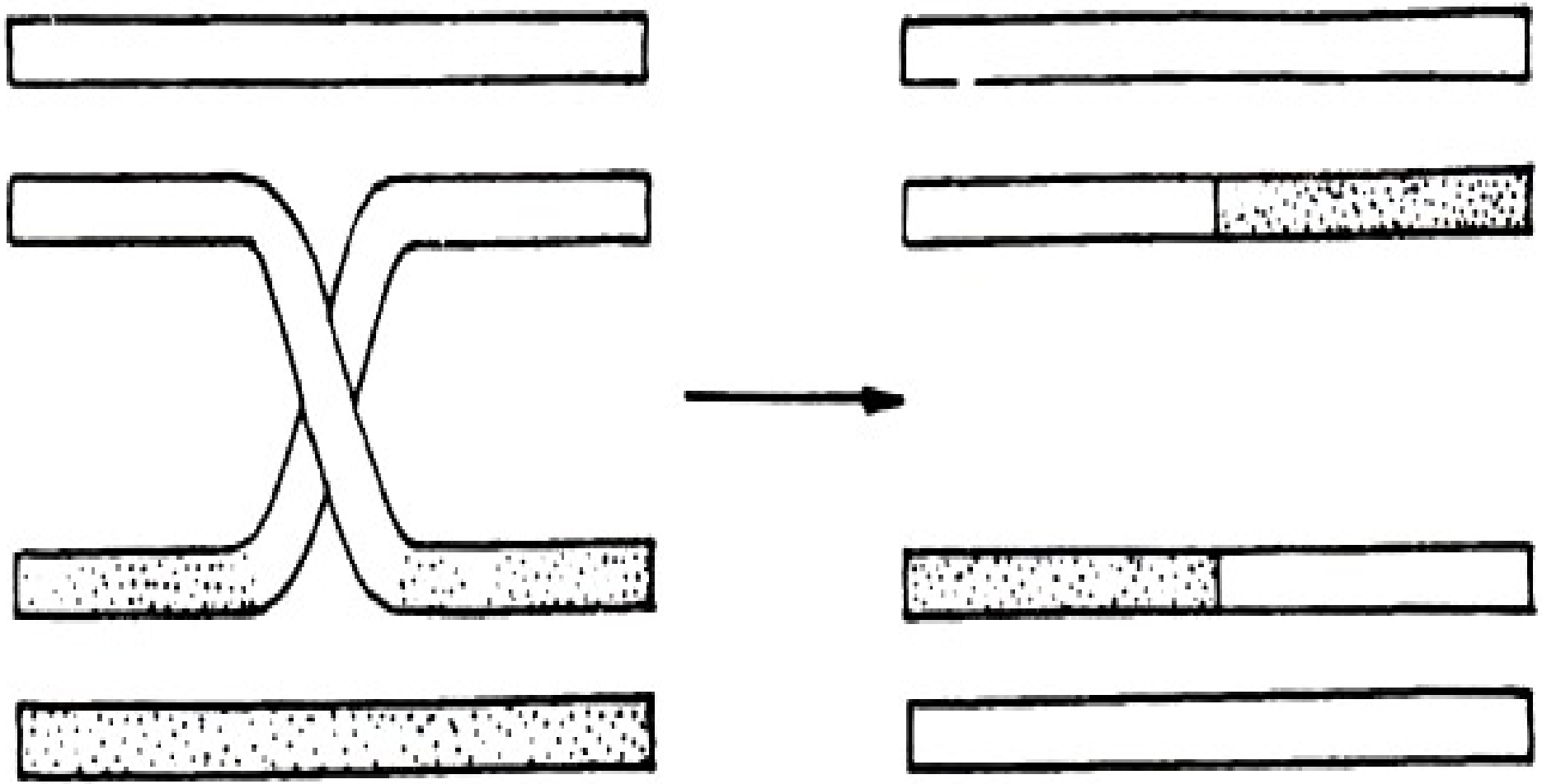


Fig. 9.1. Crossing over according to copy choice theory.

This theory has two objections:

1. According to this theory breakage and reunion does not occur, while it has been observed cytological.

2. Generally crossing over takes place after DNA replication but here it takes place at the same time.

Breakage and Reunion Theory:

This theory states that crossing over takes place due to breakage and reunion of non-sister chromatids. The two segments of parental chromosomes which are present in recombinants arise from physical breaks in the parental chromosomes with subsequent exchange of broken segments (Fig. 9.2).

The breakage results due to mechanical strains that result from the separation of paired homologous chromosomes and chromatids in each chromosome during pachytene stage. The broken ends of non-sister chromatids unite to produce chiasmata resulting in crossing over.

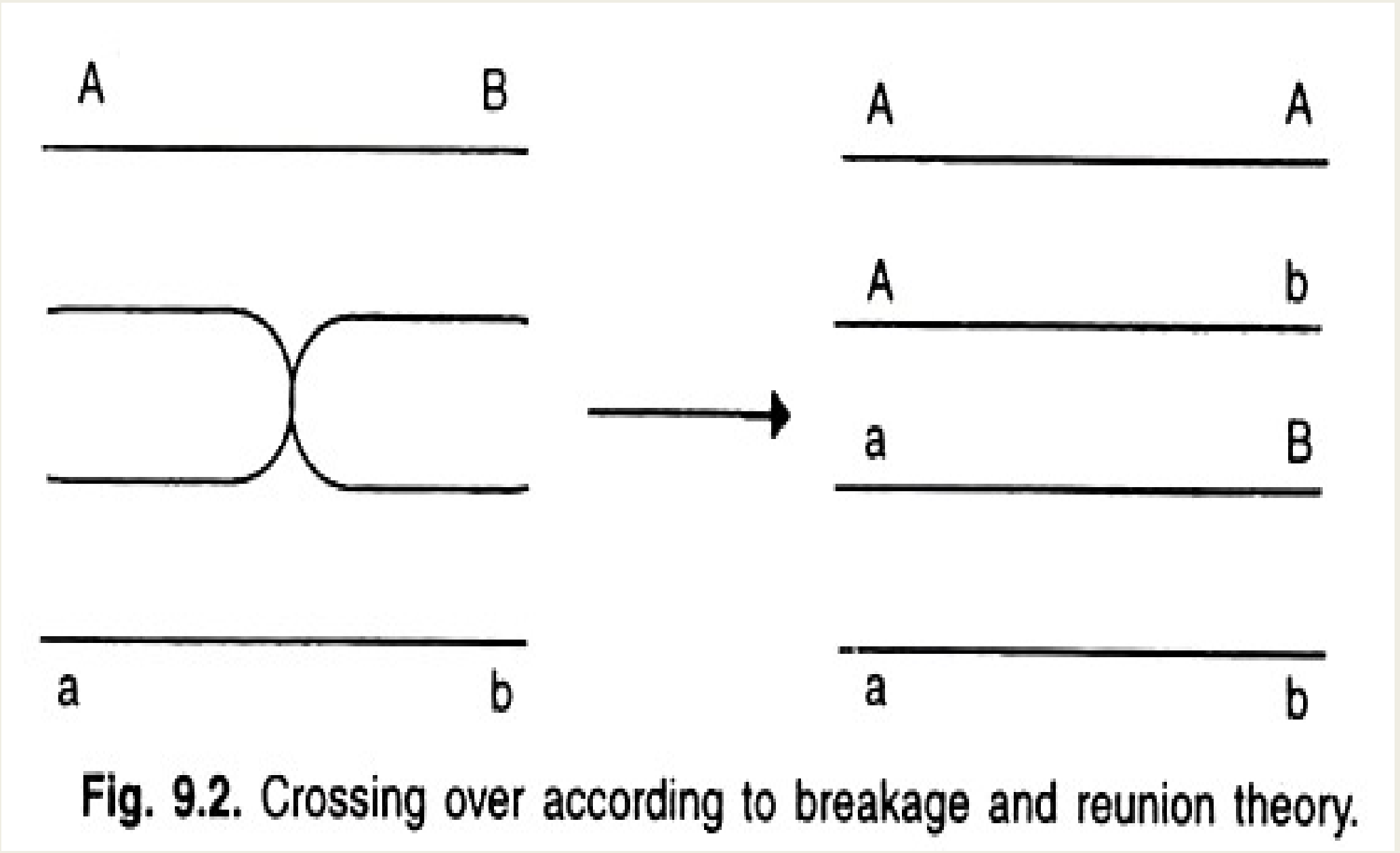


Fig. 9.2. Crossing over according to breakage and reunion theory.

Interference:

The term interference was coined by Muller which refers to the tendency of one crossover to reduce the chance of another crossover in its adjacent region. Interference is affected by gene distance on the chromosome. Lesser the gene distance greater is the interference and vice versa. Generally, it is observed that crossing over in one region of chromosome may check the crossing over in the second region.

Sometimes, presence of recombination in one region enhances the chance of recombination in another adjacent region. This is termed as negative interference. This type of situation has been observed in some lower organisms, viz., Aspergillus and bacteriophages.

Coefficient of interference is estimated as follows:

Coefficient of interference (%) = 1 – Coefficient of coincidence x 100

Positive and negative interference differ from one another in three main aspects (Table 9.2).

TABLE 9.2. Differences between positive and negative interference

Positive Interference	*Negative Interference*
1. One crossover reduces the chance of another crossover in the adjacent region.	1. One crossover enhances the chance of another crossover in the adjacent region.
2. Observed in both eukaryotes and prokaryotes.	2. Found in some lower organisms like Aspergillus and bacteriophages.
3. In this case coefficient of coincidence is less than one.	3. In this case coefficient of coincidence is always more than one.

Coincidence:

This term was also coined by Muller to explain strength or degree of interference. The coefficient of coincidence is the percentage ratio of observed double crossovers to the expected double crossovers. The greater the coincidence, lesser will be the interference and vice versa. Thus,

$$\text{Coefficient of coincidence (\%)} = \frac{\text{Observed double crossovers}}{\text{Expected double crossovers}} \times 100$$

Coefficient of coincidence is a measure of the intensity of interference, because it has negative association with interference. The value of the coefficient of coincidence is less than 1 for positive interference, greater than 1 for negative interference, 1 for absence of interference and zero for complete or absolute interference.

Chromosome Mapping:

Chromosome map refers to a line diagram which depicts various genes present on a chromosome and recombination frequency between them. Such maps are also known as genetic maps or linkage maps. The process of assigning genes on the chromosomes is known as chromosomal mapping.

The mapping of chromosomes is done with the help of three point test cross. A three point test cross is a cross of a trihybrid (F1 differing in three genes) with its homozygous recessive parent.

The three point test cross provides useful information on two important aspects, viz:

(1) About the sequence of genes, and

(2) About the recombination frequencies between genes. This information is essential for mapping of chromosomes.

5. Types of Crossing Over:

Depending upon the number of chiasmata involved, crossing over may be of three types, viz., single, double and multiple as described below:

i. Single Crossing Over:

It refers to formation of a single chiasma between non-sister chromatids of homologous chromosomes. Such cross over involves only two chromatids out of four.

ii. Double Crossing Over:

It refers to formation of two chiasmata between non-sister chromatids of homologous chromosomes. Double crossovers may involve either two strands or three or all the four strands. The ratio of recombinants and parental types under these three situations are observed as 2:2:3:1 and 4 : 0, respectively.

iii. Multiple Crossing Over:

Presence of more than two crossovers between non-sister chromatids of homologous chromosomes is referred to as multiple crossing over. Frequency of such type of crossing over is extremely low.

6. Factors Affecting Crossing Over:

The frequency of crossing over is influenced by several factors which are briefly discussed below:

i. Distance:

The distance between genes affects the frequency of crossing over. Greater the distance between genes higher is the chance of crossing over and vice versa.

ii. Age:

Generally crossing over decreases with advancement in the age in the female Drosophila.

iii. Temperature:

The rate of crossing over in Drosophila increases above and below the temperature of 22°C.

iv. Sex:

The rate of crossing over also differs according to sex. There is lack of crossing over in Drosophila male and female silk moth.

v. Nutrition:

Presence of metallic ions like calcium and magnesium in the food caused reduction in recombination in Drosophila. However, removal of such chemicals from the diet increased the rate of

vi. Chemicals:
Treatment with mutagenic chemicals like alkylating agents was found to increase the frequency of crossing over in Drosophila female.
vii. Irradiation:

Irradiation with X-rays and gamma rays was found to enhance the frequency of crossing over in Drosophila females.

viii. Structural Changes:
Structural chromosomal changes especially inversions and translocations reduce the frequency of crossing over in the chromosomes where such changes are involved.

ix. Centromere Effect:

Generally genes that are located adjacent to the centromere show reduced frequency of crossing over.

x. Cytoplasmic Genes:

In some species cytoplasmic genes also lead to reduction in crossing over. For example, Tifton male sterile cytoplasm in pearl millet.

7. Cytological Proof of Crossing Over:

The first cytological evidence in support of genetic crossing over was provided by Curt Stern in 1931 on the basis of his experiments conducted with Drosophila. He used cytological markers in his studies. He selected a female fly in which one X-chromosome was broken into two segments.

Out of these two segments, one behaved as X-chromosome. The other X-chromosome had small portion of Y-chromosome attached to its one end. Thus, both the X-chromosomes in the female had distinct morphology and could be easily identified under microscope. In female fly, the broken X-chromosome had one mutant allele (carnation) for eye colour and another dominant allele (B) for bar eye shape.

The other X-chromosome with attached portion of Y chromosome had alleles for normal eye colour (red eye) and normal eye shape (oval eye). Thus, phenotype of female was barred. A cross of such females was made with carnation male (car+).

As a result of crossing over female flies produce four types of gametes, viz., two parental types or non-crossover types (car B and ++) and two recombinant types or crossover types (car+ and B+).

The male flies produce only two types of gametes (car + and Y), because crossing over does not take place in Drosophila male. A random union of two types of male gametes with four types of female gametes will produce males and females in equal number, means there will be four females and four males (Fig. 9.4).

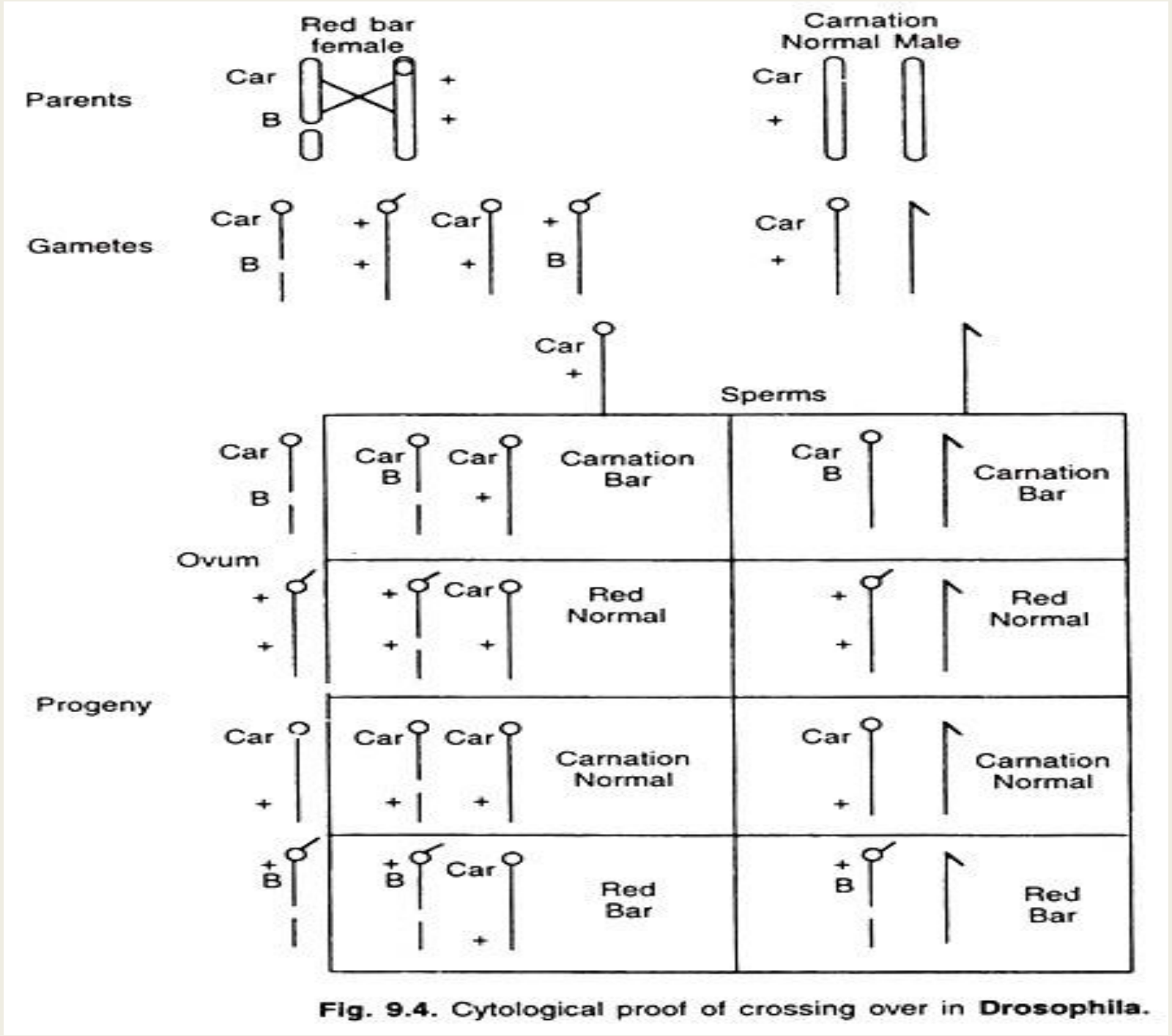


Fig. 9.4. Cytological proof of crossing over in **Drosophila.**

Stern examined the chromosomes of recombinant types, viz., red bar and carnation normal under microscope. He observed that in carnation normal females both the X-chromosomes were of equal length. In red bar flies, one X-chromosome was normal and other was fragmented.

The fragmented X-chromosome also had attached part of Y-chromosome. Such chromosome combination in red bar is possible only through exchange of segments between non-sister chromatids of homologous chromosomes. This has proved that genetic crossing over is the result of cytological crossing over. Similar proof of cytological crossing over was provided by Creighton and McClintock in maize.

8. Significance of Crossing Over:

Crossing over is useful in three principal ways, viz:

(1) Creation of variability,

(2) Locating genes on the chromosomes, and

(3) Preparing linkage maps as described below:

i. Creation of Variability:

Crossing over leads to recombination or new combination and thus is a potential genetic mechanism for creating variability wh

essential for improvement of genotypes through selection.

ii. Locating Genes:

Crossing over is a useful tool for locating genes in the chromosomes.

iii. Linkage Maps:

Crossing over plays an important role in the preparation of chromosome maps or linkage maps. It provides information about frequency of recombination's and sequence of genes which are required for preparation of linkage maps.

3.SEX LINKAGE..SEXLINKED INHERITANCE

Sex linkage describes the sex-specific patterns of inheritance and presentation when a gene mutation (allele) is present on a sex chromosome (allosome) rather than a non-sex chromosome (autosome). In humans, these are termed X-linked recessive, X-linked dominant and Y-linked.

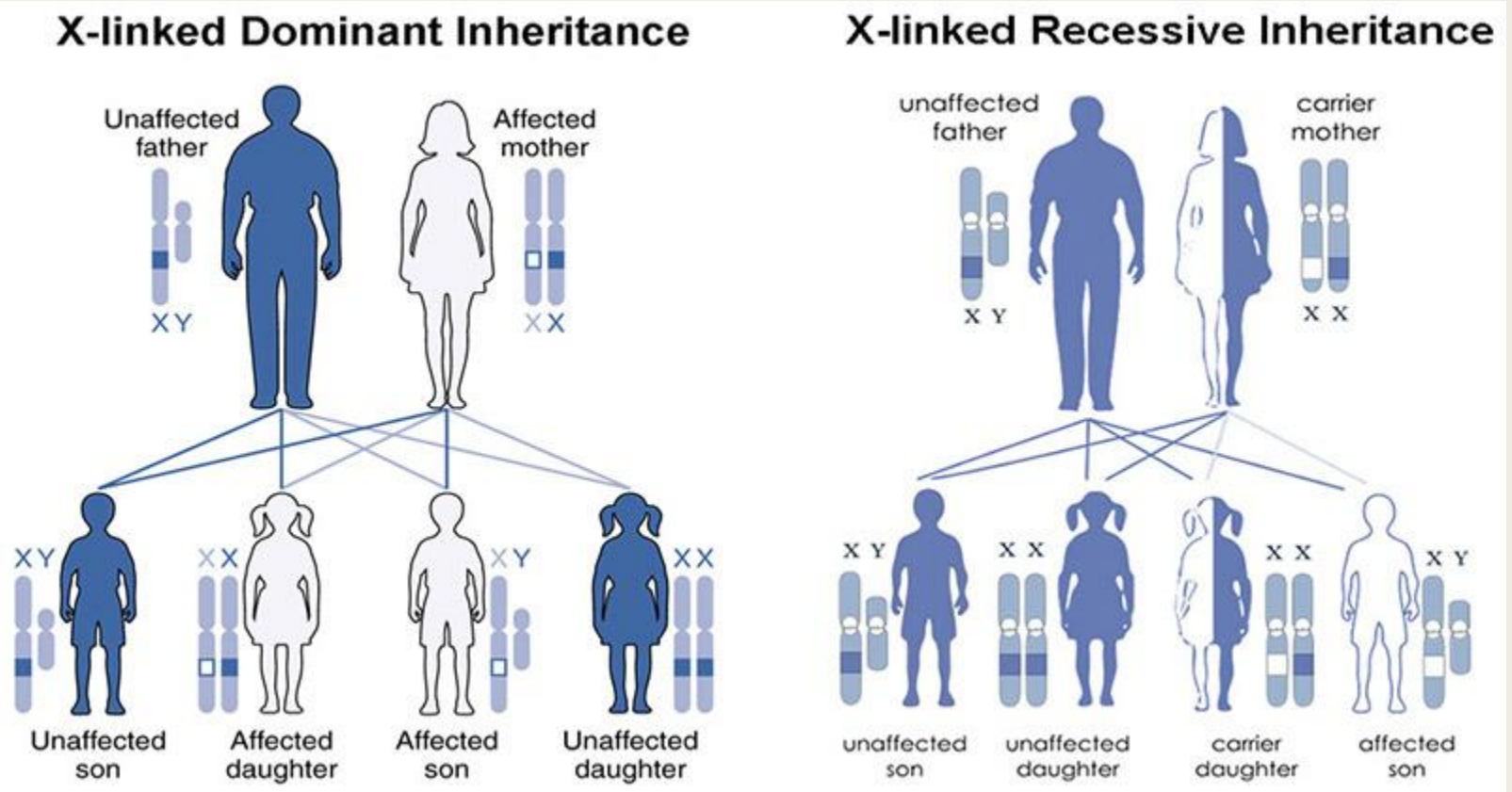
Sex-linked Inheritance

Sex makes no difference in Mendel's crosses. But the Mendel's laws are not applicable on those genes which are exclusively located either in X or Y chromosome.

Sex-Linked Inheritance is the inheritance of a trait (phenotype) that is determined by a gene located on one of the sex chromosomes.

The genes which occur exclusively on the X chromosome or on the analogous Z chromosome (in birds and other species) are called X- or Z -linked genes while the genes which exclusively occur in Y chromosome are called holandric genes.

The inheritance of such X- or Z-linked and holandric genes is called sex-linked inheritance.


X-linked Dominant Inheritance
Unaffected father
Affected mother
XY
XX
XY
XX
XY
XX
Unaffected son
Affected daughter
Affected son
Unaffected daughter
X-linked Recessive Inheritance
unaffected father
carrier mother
X Y
X X
X Y
X X
X X
X Y
unaffected son
unaffected daughter
carrier daughter
affected son

Characteristics of Sex-linked Inheritance

It has been observed that the genes occurring only in the X chromosomes are represented twice in female (because female contains 2X chromosomes) and once in male (because male has only one X chromosome).

The differential region of each chromosome (i.e., X) contain genes that have no counterparts on the other kind of sex chromosome. These genes, whether dominant or recessive, show their effects in the male phenotype. Genes in the differential regions are called hemizygous (“half zygous”) in the males.

Inheritance of X-Linked Recessive Genes

The X-linked recessive genes show criss-cross pattern of inheritance.

In criss-cross inheritance, an X-linked recessive gene is transmitted from P1 male parent (father) to F2 male progeny (grandsons) through its F1 heterozygous females (daughters), which are called carriers) and different F1 and F2 results (ratios) in the reciprocal crosses.

The X-linked recessive phenotype is usually found more frequently in the male than in the female. This is because an affected female can result only when both mother and father bear the X-linked recessive allele (e.g., XA Xa × Xa Y), whereas an affected male can result when only the mother carries the gene.

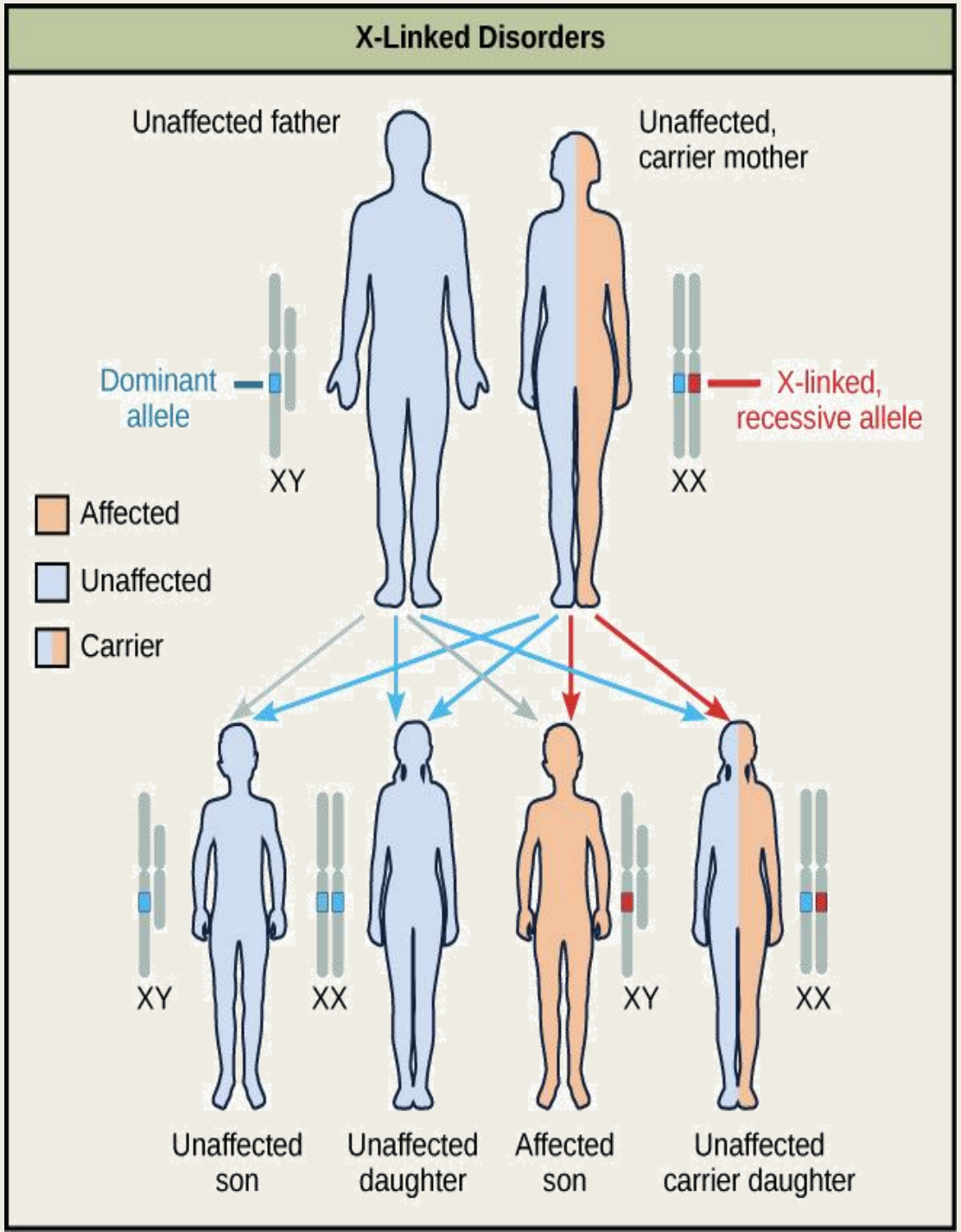
Usually none of the offspring of an affected male will be affected, but all his daughters will carry the gene in masked heterozygous condition, so one half of their sons (i.e., grandsons of F1 father) will be affected.

None of the sons of an affected male will inherit the X-linked recessive gene, so not only will they be free of the defective phenotype; but they will not pass the gene along to their offspring.

Example

In Drosophila, the gene for white eye colour is X linked and recessive to another X-linked, dominant gene for red-eye colour.

When white-eyed male was mated with a red-eyed female the F1 flies were all red-eyed. F2 generation of it included 3: 1 ratio of red and white-eyed flies. But all white eyed flies of F2 generation were males only. When normal female of F1 is crossed with normal male 50% of males were white-eyed and 50% were red-eyed It shows that the recessive allele is expressed in male only. The common sex-linked disorders that are mostly found in humans are mostly recessive. They include disorders like Color-blindness and Haemophilia.


X-Linked Disorders
Unaffected father
Unaffected,
carrier mother
Dominant
allele
X-linked,
recessive allele
XY
XX
Affected
Unaffected
Carrier
XY
XX
XY
XX
Unaffected
son
Unaffected
daughter
Affected
son
Unaffected
carrier daughter

Colour-blindness

It is a defect in which a person cannot distinguish between red, green or both the colours from other colours.

Haemophilia (Bleeder's disease)

Haemophilia is called a royal disease and known as the most serious of all the diseases. A person suffering from this disease have the inability of their blood to clot normally even after a minor injury. It is due to the lack of a blood protein called clotting factor VIII and clotting factor IX.

Inheritance of X-Linked Dominant Genes

Dominant X-linked genes are detected more frequently found in the female than in the male of the species.

The affected males pass the condition on to all of their daughters but to none of their sons.

Females usually pass the condition (defective phenotype) on to one-half of their sons and daughters.

A X-linked dominant gene fails to be transmitted to any son from a mother which did not exhibit the trait itself.

Human Disorders

In humans, X-linked dominant conditions are relatively rare.

One example is hypophosphatemia (vitamin D-resistant rickets).

Another example includes hereditary enamel hypoplasia (hypoplastic amelogenesis imperfecta), in which tooth enamel is abnormally thin so that teeth appear small and wear rapidly down to the gums

Inheritance of Y-Linked Genes

Genes in the non-homologous region of the Y chromosome pass directly from male to male.

In man, the Y-linked or holandric genes are transmitted directly from father to son.

Example

Genes for ichthyosis hystrix gravis hypertrichosis (excessive development of hairs on pinna of ear)

Genes for H-Y antigen, histocompatibility antigen, spermatogenesis, height(stature) and slower maturation of individual.

CHROMOSOMAL SEX DETERMINATION

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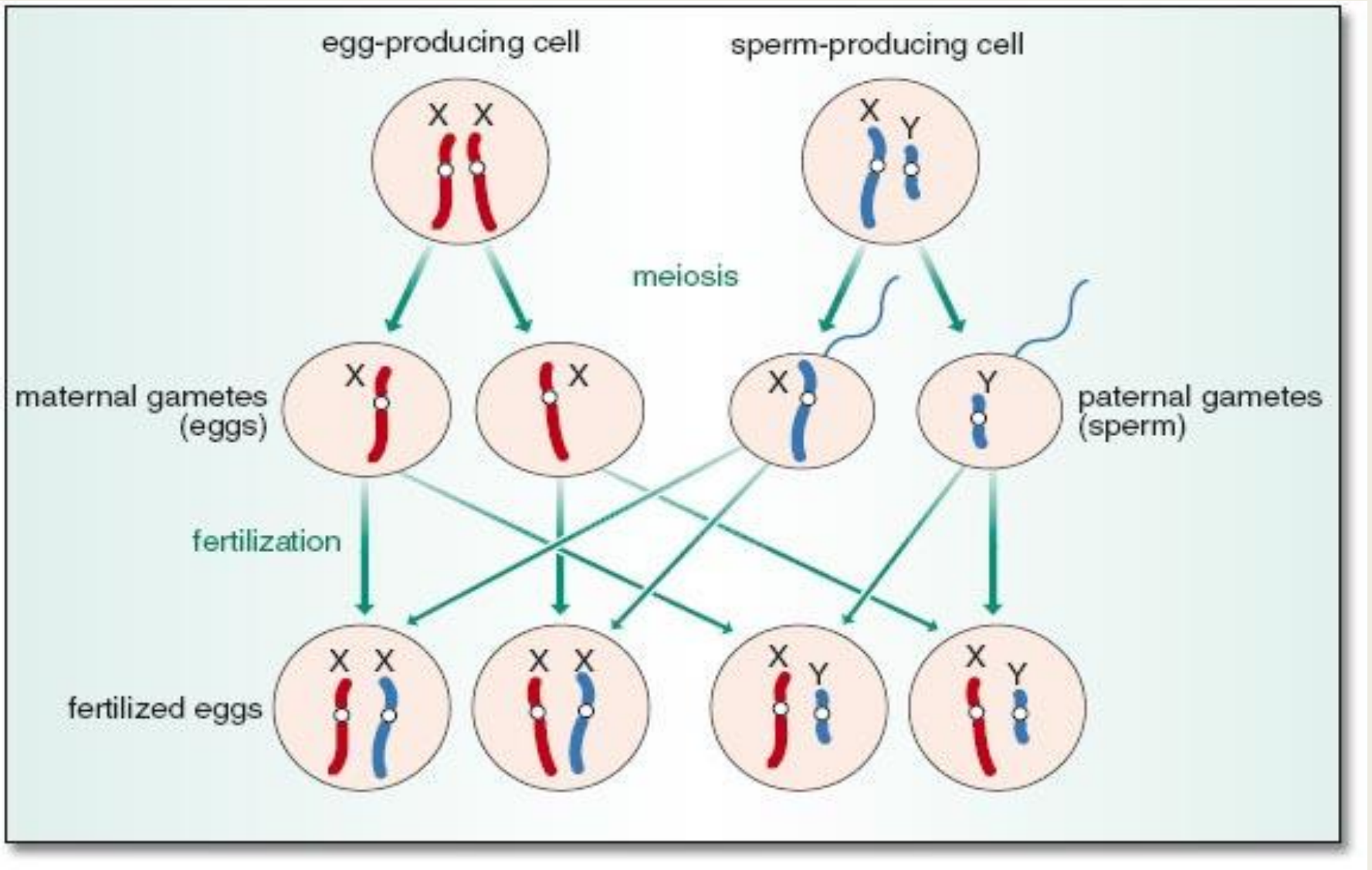


Sex Determination

Fixing the sex of an individual as it begins life is called sex determination. The various genetically controlled sex-determination mechanisms have been classified into following categories

(i) **Chromosomal theory of sex determination:** The X-chromosome was first observed by German biologist, **Henking** in 1891 during the spermatogenesis in male bug and was described as X-body. The chromosome theory of sex determination was worked out by **E.B. Wilson** and **Stevens** (1902-1905). They named the X and Y chromosomes as sex-chromosomes or allosomes and other chromosomes of the cell as autosomes.

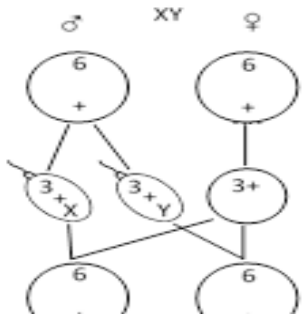
Sex chromosomes carry genes for sex. X-chromosomes carries female determining genes and Y-chromosomes has male determining genes. The number of X and Y chromosomes determines the female or male sex of the individual, Autosomes carry genes for the somatic characters. These do not have any relation with the sex.

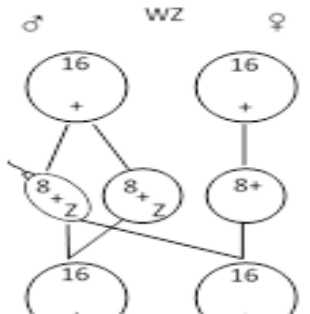
(a) **XX-XY type or Lygaeus type :** This type of sex-determining mechanism was first studied in the milk weed bug, Lygaeus turcicus by **Wilson** and **Stevens**. Therefore, it is called Lygaeus type. These are two different patterns of sex determination in Lygaeus type.

(1) **Female homogametic XX and male heterogametic XY :** The homogametic sex (XX) is female and produces ova all of one type, *i.e.* having X-chromosome. The male is heterogametic-XY and produces sperm of two types. 50% of which possess X-chromosome and other 50% Y-chromosome. This is simple XX-XY type and is found in man, *Drosophila* and certain insects.

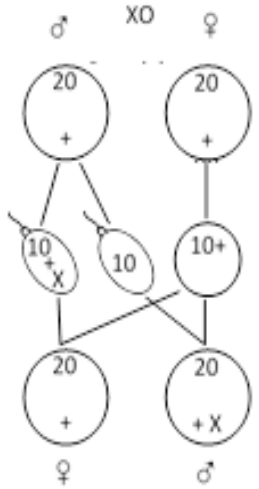
Example : In *Drosophila* total number of chromosomes is eight, of which six are autosomes, common to both male and female. The fourth pair is of sex chromosomes. In male this is represented by XY *i.e.* Karyotype of male *Drosophila* 6+XY and in female XX *i.e.* 6+XX. Ova produced by female are all similar possessing 3+X chromosomes, whereas the sperm produced by male are 3+X and 3+Y in equal numbers.

(2) **Female heterogametic and male homogametic :** In fowl, other birds and some fishes, certain moths and butterflies, the female sex is heterogametic, with X and Y chromosome often represented by Z and W and laying two types of eggs, one half with X or Z chromosome and the other half with Y or W chromosome. The male sex is homogametic having XX or ZZ chromosomes. It produces sperm all of one type.





(b) **XX-XO type or Protenor type : Mc clung** in male squash bug (*Anasa*) observed 10 pairs of chromosomes and an unpaired chromosome. Their females have eleven pairs of chromosomes (22). Thus all the eggs carry a set of eleven chromosomes but the sperm are of the two types: fifty percent with eleven chromosomes and the other fifty percent with ten chromosomes. The accessory chromosome was X-chromosomes. Fertilization of an egg by a sperm carrying eleven chromosomes results in a female, while its fertilization by a sperm with ten chromosomes produces male. It is said to be evolved by the loss of Y-chromosome.



(c) **Haploid-diploid mechanism of sex determination:** Hymenopterous insects, such as bees, wasps, saw flies, and ants, show a unique phenomenon in which an unfertilized egg develops into a male and a fertilized egg develops into a female. Therefore, the female is diploid (2N), and the male is haploid (N). eggs are formed by meiosis and sperms by mitosis. Fertilization restores the diploid number of chromosomes in the zygote which gives rise to the female. If the egg is not fertilized, it will still develop but into a male. Thus, the sex is determined by the number of chromosomes.

In honeybee, the quality of food determines whether a diploid larva will become a fertile queen or a sterile worker female. A larva fed on royal jelly, a secretion from the mouth of nursing workers, grows into a queen, whereas a larva fed on pollen and nectar grows into a worker bee. Thus, the environment determines fertility or sterility of the bee but it does not alter the genetically determined sex. The sex ratio of the offspring in the hive is controlled by the queen. She lays more fertilized eggs that produce worker females and fewer unfertilized eggs which produce haploid males. The queen mates only once in her life time, keeps a store of sperms in the seminal receptacle, and can control fertilization of eggs by releasing or not releasing sperms.

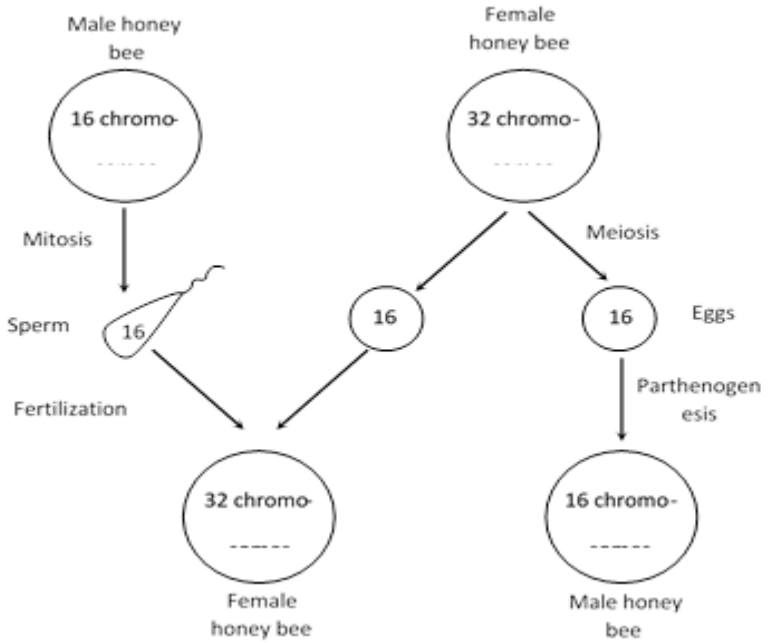


Fig : Haploid-diploid mechanism of sex determination in honeybee

Different types of chromosomal mechanisms of sex-determination in animals

S. No.	Organisms	Heterogametic sex	Gamete		Zygotes	
			Sperms	Eggs	Females	Males
(1)	*Drosophila*, man etc.	Male	X and Y	All X	XX	XY
(2)	Protenor(Bug, Grasshopper)	Male	X and O	XX	XX	XO
(3)	Birds, moths	Female	All X	X and Y	XY	XX
(4)	Fumea (a moth)	Female	All X	X and O	X	XX

(ii) **Quantitative or ratio theory of sex determination: C.B Bridges** worked out ratio theory of sex determination in *Drosophila*. According to this theory the ratio of chromosomes to autosomes is the determining factor for the sex. Single dose of X-chromosome in a diploid organism produces male, whereas 2X-chromosomes produce a female. If a complete haploid set of autosomes is designated by A then 2A : X will give rise to male and 2A : 2X to female.

(a) **Intersexes in *Drosophila* and ratio theory of sex determination:** Bridges hypothesis was supported by studies of flies arising after abnormal distribution of chromosomes on account of non-disjunction. Due to abnormal meiosis during oogenesis both the X-chromosomes fail to separate and move to one pole of meiotic spindle. Thus few eggs are formed with single autosomal genome but with 2X chromosomes, *i.e.* (AXX) and other with single autosomal genome but no sex chromosome (A). when such abnormal eggs are fertilized with normal sperm, the following result are obtained.

Results of fertilization of abnormal female gametes

AAXXY - Female

AAXXX - Super female

AAX - Sterile male

AAY - Nonviable

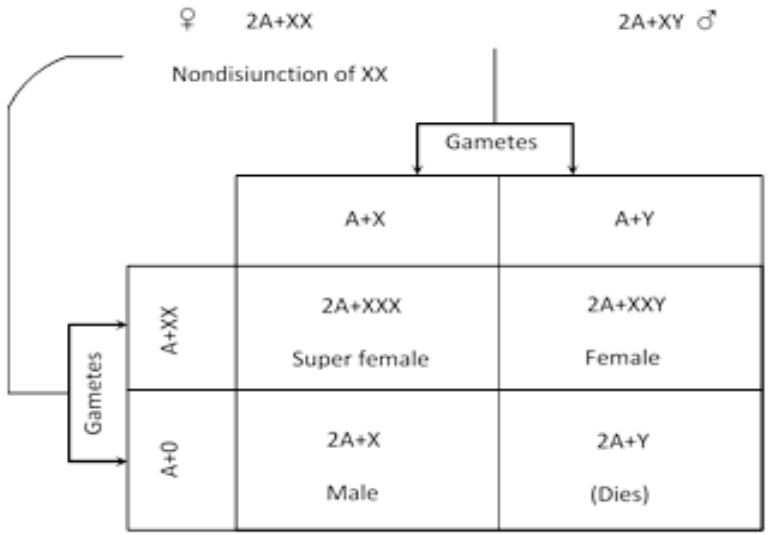


Fig : Nondisjunction of X-chromosome in a female Drosophila leading to transfer of both X-chromosomes to one egg

Out of this progeny 1/4th males with no X are nonviable; the other 1/4 are without Y-chromosome and sterile. 1/4th females have an extra Y-chromosome while rest 1/4th females with 3X are super females. These are sterile with under developed sexual characteristics.

(ii) **Triploid intersexes and balance theory:** The triploid flies with (3A + 3X) are much like the normal diploid females both in appearance as well as in fertility. On mating to diploid males their progeny consisted of following types.

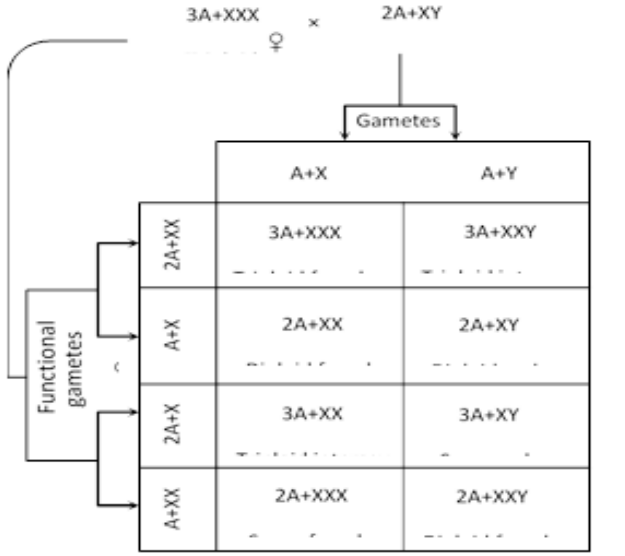


Fig : Results of a cross between triploid female and diploid male

(1) AAAXXX - Triploid females

(2) AAXX - Dilpoid females

(3) AAXXY - Diploid females

(4) AAAXX - Intersexes

(5) AAAXXY - Intersexes

(6) AAXY - Normal ills

(7) AAXXX - Super females

(8) AAAXY - Super males

The intersexes are sterile and intermediate between females and male, because the sex balance ratio in the intersexes comes to 2 : 3.

(2) **Gyandromorphs in Dorsophila and ratio theory of sex determination:** In *Drosophila* occasionally flies are obtained in which a part of the body exhibits female characters and the other part exhibits male characters. Such flies are known as **gynandromorphs**. These are formed due to misdivision of chromosomes and start as female with 2A+2X-chromosomes. One of the X-chromosomes is lost during the division of the cell with the result that one of the daughter cells possesses 2A+2X chromosomes and the other 2A+X. If this event happens during first zygotic division, two blastomeres with unequal number of X-chromosomes are formed. The blastomere with 2A+2X-chromosomes develops into female half, while the second blastomere with 2A+X chromosomes produces male half and the resultant fly is a bilateral gynandromorph. The occurrence of gynandromorphs clearly indicates that the number of X-chromosomes determines the sex of the individual.

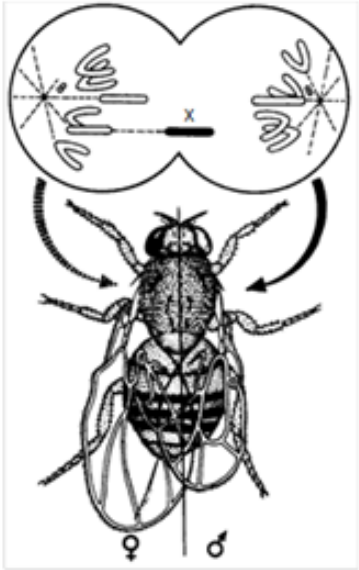


Fig : Gynandromorph of Drosophila in which right half is male and left half is female

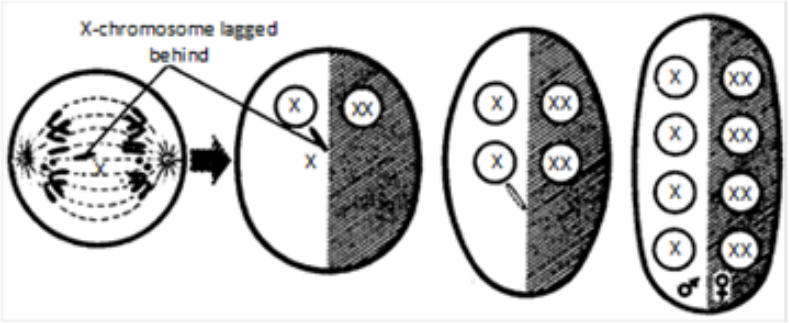


Fig : Diagram to show origin of gynandromorphs

(iii) **Genic balance theory :** Based upon the observations of ratio theory **Bridges** put forward genic balance theory in which he suggested that every individual whether male or female possesses in its genotype genes for both male and female characteristics. Which sex will actually develop is decided by the preponderance of that type of genes.

According to the genic balance theory of Bridges in *Drosophila melanogaster*, sex is determined by the ratio of the X-chromosomes and the set of autosomes. The *Y*-chromosomes play no part in sex determination it only governs male fertility. The XO flies are male, but sterile. Sex is governed by the ratio of the number of X chromosomes to sets of autosomes. The table given below indicates how the ratio of X/A help to determine the sex.

Ratio of X-chromosome to autosomes and the corresponding phenotype in *Drosophila*

S. No.	Sex	Number of X-chromosomes	Number of autosomal set	Sex index X/A ratio
(1)	Super female	XXX (3)	AA (2)	3/2 = 1.5
(2)	Normal female Tetraploid Triploid Diploid Haploid	XXXX (4) XXX (3) XX (2) X (1)	YYYY (4) AAA (3) AA (2) A (1)	4/4 = 1.0 3/3 = 1.0 2/2 = 1.0 1/1 = 1.0
(3)	Intersex	XX (2)	AAA (3)	2/3 = 0.66
(4)	Normal male	X (1)	AA (2)	1/2 = 0.50
(5)	Super male	X (1)	AAA (3)	1/3 = 0.33

Genes for maleness are carried on the autosomes, those for femaleness on the X-chromosomes. The sex index ratio of female is 1.0 while in males is 0.50. If X/A ratio is greater than 1.0 produces super females (meta females) and less than 0.50 produces super males. The X/A ratio lesser than 1.0 but greater than 0.5 (for example 0.66) result in intersexes. The degree of femaleness is greater where the X/A ratio is closer to 1.0 and the degree of maleness is greater where that ratio is closer to 0.5.

Human sex determination : The genic balance theory of sex determination is not universally accepted. Unlike *Drosophila* X : A does not influence sex determination. The key to sex determination in humans is the SRY (for sex region on the Y) gene located on the short arm of the Y-chromosome. In the male, the testis-determining factor (TDF) is produced by SRY on the Y-chromosome. TDF induces the medulla of the embryonic gonads to develop into testes. In the absence of SRY on Y, no TDF is produced. The lack of TDF allows the cortex of the embryonic gonads to develop into ovaries.

(iv) **Hormonal theory of sex determination :** The sex determination theories of chromosomes and genic balance successfully apply to the lower animals but in higher vertebrates and under certain conditions in invertebrates, the embryo develops some characters of the opposite sex together with the characters of its own sex-chromosome. It means, the sex changes under specific circumstances. This is due to the hormones secreted by the gonads of that animal.

(a) **Free martinism :** The influence of hormones on sex determination comes from free-martins often found in cattles. LILLIE and others found that where twins of opposite sex (one male and other female) are born, the male is normal but female is sterile with many male characteristics. Such sterile females are known as free martins.

The scientific explanation for the formation of free martins is the effect of hormones of the male sex on the female. In cattle the foetal membranes of the twins are fused in such a manner that they have a common circulation of blood. The female hormone is produced at a slightly later stage in the development and guides its development towards female side. But since the twins have a common circulation and blood passes from one twin into the body of other twin, the male hormone which is produced slightly in advance of female hormone, enters the body of female twin and before the female hormone onsets the development of female characteristics it is already differentiated in the guidance of male hormone. As a result the developing female is sterile.

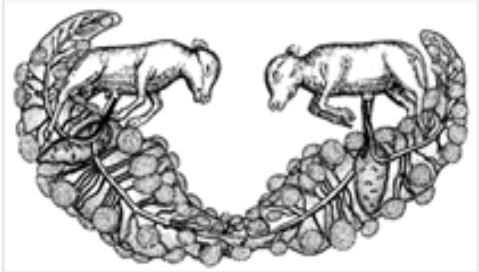


Fig : Free martins in cattle

(v) **Environmental theory of sex determination :** In some animals, there is environmental determination of sex.

(a) In *Bonellia*, a marine worm, the swimming larva has no sex. If it settles down alone, it develops into a large (2.5 *cm*) female. If it lands on or near an existing female proboscis, a chemical secreted from her proboscis causes the larva to develop into a tiny (1.3 *mm*) male. Male lives as a parasite in the uterus of the female.

(b) In turtles, a temperature below 28°C produces more males, above 33°C produces more females, and between 28°C to 33°C produces males and females in equal proportion, while in crocodile male sex is predominant at high temperature.

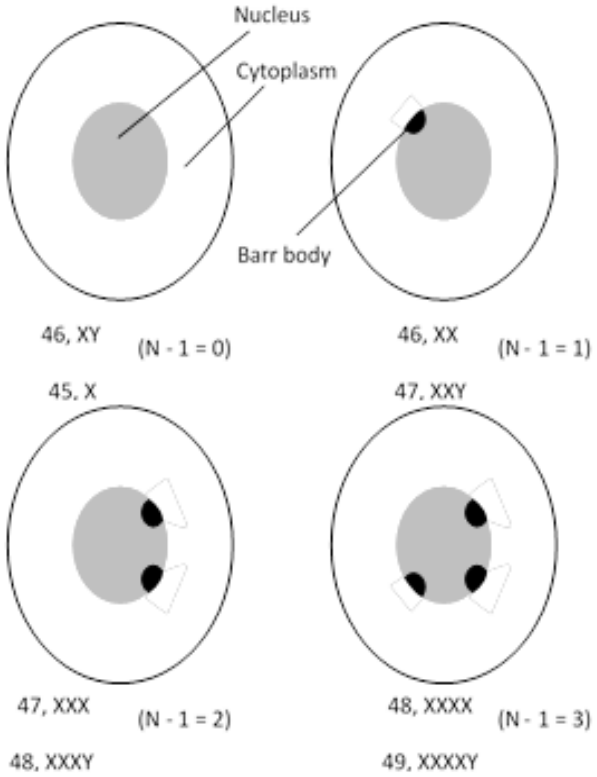


Fig : Chromosome variations and Barr body

(vi) **Barr body in sex determination : Murray Barr** (1949), a geneticist noticed a small body in the nucleus of the nerve cells of female cats which stained heavily with nuclear stains. Further investigations showed that not only nerve cells, but many other cells from female cats only, had these bodies, now known as sex chromatin or Barr bodies. It was soon learnt that such bodies can be found in females of many mammals including human. In women the Barr body lies against the nuclear membrane like a round disc in the neutrophil blood cells, skin cells, nerve cells, cells of mucous membrane, cells of lining in vagina and urethra. They are absent in man. These bodies are thus named after the discover **Barr**.

Barr bodies are used to determine the sex of unborn human embryos. In this technique called **amniocentesis** sample of the amniotic fluid is examined for Barr bodies. The sex is determined by the presence or absence of Barr bodies in epithelial cells of embryo present in the amniotic fluid sample. Studies from the cells of aborted embryos show that Barr bodies can be distinguished at about 15 or 16^{th} day after conception that means several weeks before the formation of gonads. Whereas sex of embryo is determined soon after fertilization, sex differentiation can be noticed in third week stage of pregnancy.

Mary Lyon hypothesis : According to the British geneticist **Mary Lyon** (1961), one of the two X-chromosomes of a normal female becomes heterochromatic and appears as Barr body. This inactivation of one of the two X-chromosomes of a normal female is the dosage compensation or Lyon's hypothesis.

It is estimated that number of Barr bodies is one less from the total number of X chromosomes present in embryo. Therefore, Barr bodies are also used to decide the genic constitution of such persons who have irregular number of sex chromosomes. More than one X chromosome in such persons is transformed into Barr bodies.

S. No.	Individual	No. of X chromosome	No. of Barr body (X - 1)
(1)	Normal woman	XX	2-1 = 1 (one barr body)
(2)	Women with Turner's syndrome	XO	1-1 = 0 (no barr body)
(3)	Super female	XXX	3-1 = 2 (two barr bodies)
(4)	Man	XY	1-1 = 0 (no barr body)
(5)	Man with Klinefelter's syndrome	XXY	2-1 = 1 (one barr body)

Sex can also be distinguished by studies of simple blood smears. The neutrophils, the most common of the white blood corpuscles, have a nucleus divided into two or three lobes. Female neutrophils showing a small drumstick extending out from one of the nuclear lobes, is a definite indication of the female chromosome component in the cells.

Important Tips

- *Goldschmidt brought forward the quantitative theory of sex..*
- *The term "gynandromorphism" was introduce by Goldschmidt in 1915.*
- *Drumstick is the sex chromatin present in the neutrophil (Polymorphonuclear leucocyte) of 3 to 5% cells in females, but not in males.*
- *Y chromatin (Y body) can be identified as bright spot by staining cells with acridine dyes.*
- *First X-linked gene was discovered by T.H. Morgan (1910) for white eye mutation.*
- *Pedigree of colour blindness was first described by Horner (1876).*
- *It is also called bleeder's disease, first studied by John Cotto in 1803.*
- *Duchenne Muscular Dystrophy (DMD) is the disease which is characterized by a progressive weakness and loss of muscle.*
- *Inheritance of beard in a man is sex-limited.*
- *In melandrium (Garden flower) the sex determination type is XX-XY.*

VARITIES OF GENE EXPRESSION ..MULTIPLE ALLELE ..LETHAL GENE.PLEOTROPIC GENE..EPISTASIS.

MULTIPLE ALLELE

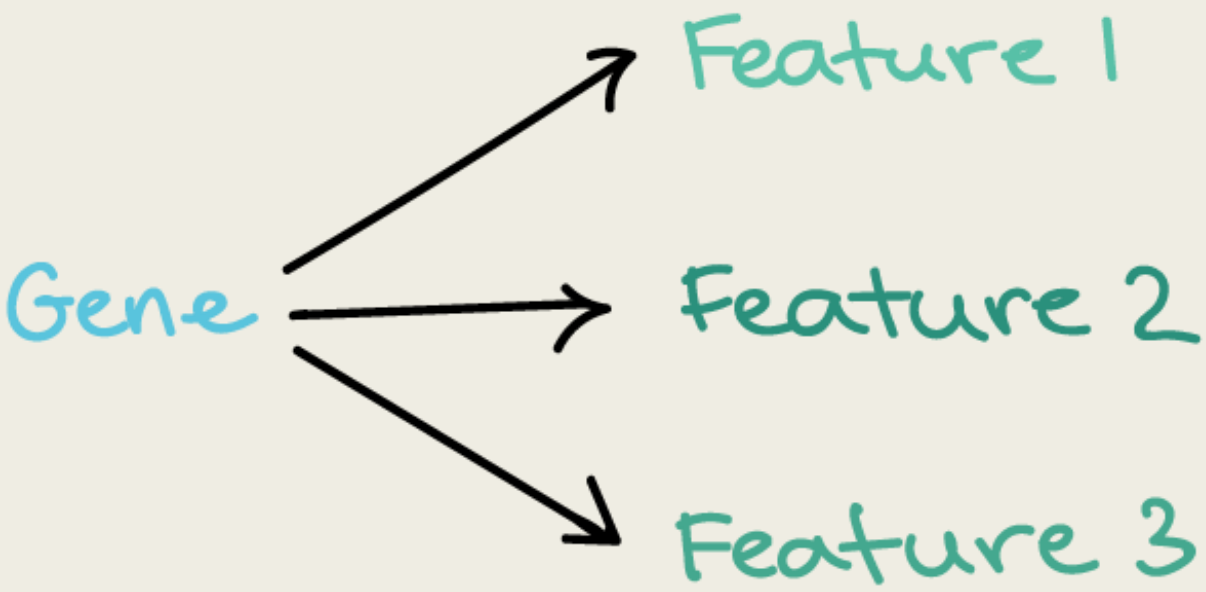
Alleles are the pairs of genes occupying a specific spot called locus on a chromosome. Typically, there are only two alleles for a gene in a diploid organism. When there is a gene existing in more than two allelic forms this condition is referred to as multiple allelism. Allelism refers to any of the several forms of a gene. These genetic variations arise usually through mutation and therefore are responsible for hereditary variations.

In particular, multiple allelism is the condition wherein three or more alleles of a gene are present. Thus, the term multiple alleles pertain to the presence of three or more alleles for a particular gene. Multiple allelism is best illustrated by the ABO blood group system in humans. In the inheritance of ABO blood group in humans, gene I (I, i.e. isohaemagglutinin) exists in three allelic forms: IA, IB, and IO. IA and IB are codominant. They are responsible for type A and type B antigens, respectively, on the cell surface of erythrocytes. IO is a recessive allele and does not produce antigen. It should be noted though that even if there are more than two alleles present in the population, the individual comprising the population would possess only two such alleles. Thus, in the case of ABO blood group system, the inheritance of IA and IB alleles results in having a blood type AB.

Pleiotropy and lethal alleles

Genes , which control multiple, seemingly unrelated features, are said to be pleiotropic (pleio- = many, -tropic = effects)phenotypes can be traced back to a defect in one gene with several jobs.

PLEIOTROPY



One gene affects multiple characteristics.

Importantly, alleles of pleiotropic genes are transmitted in the same way as alleles of genes that affect single traits. Although the phenotype has multiple elements, these elements are specified as a package, and the dominant and recessive versions of the package would appear in the offspring of two heterozygotes in a ratio of 3:1.

Pleiotropy in human genetic disorders

Genes affected in human genetic disorders are often pleiotropic. For example, people with a hereditary disorder called Marfan syndrome may have a set of seemingly unrelated symptoms, including the following^{1,3}

1,3

start superscript, 1, comma, 3, end superscript:

Unusually tall height

Thin fingers and toes

Dislocation of the lens of the eye

Heart problems (in which the aorta, the large blood vessel carrying blood away from the heart, bulges or ruptures).

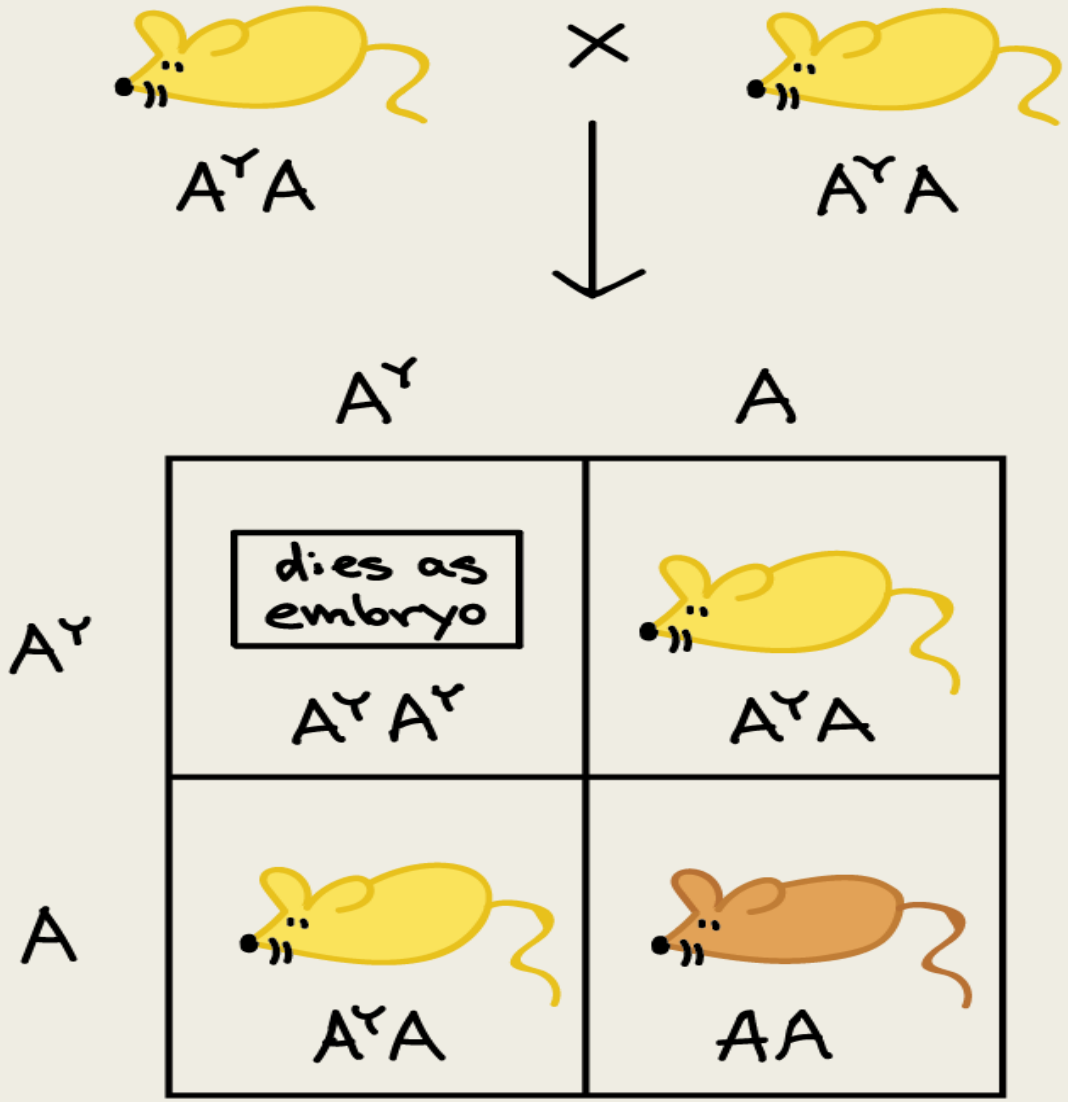
Lethality

For the alleles that Mendel studied, it was equally possible to get homozygous dominant, homozygous recessive, and heterozygous genotypes. That is, none of these genotypes affected the survival of the pea plants. However, this is not the case for all genes and all alleles. Many genes in an organism's genome are needed for survival. If an allele makes one of these genes nonfunctional, or causes it to take on an abnormal, harmful activity, it may be impossible to get a living organism with a homozygous (or, in some cases, even a heterozygous) genotype.

Example: The yellow mouse

A classic example of an allele that affects survival is the lethal yellow allele, a spontaneous mutation in mice that makes their coats yellow. This allele was discovered around the turn of the 20th century by the French geneticist Lucien Cuenót, who noticed that it was inherited in an unusual pattern

When yellow mice were crossed with normal agouti (brown) mice, they produced half yellow and half brown offspring. This suggested that the yellow mice were heterozygous, and that the yellow allele, A ^ YA
Y
A, start superscript, Y, end superscript, was dominant to the agouti allele, AAA. But when two yellow mice were crossed with each other, they produced yellow and brown offspring in a ratio of 2:1:1, colon, 1, and the yellow offspring did not breed true (were heterozygous).



2 yellow : 1 brown among survivors

Epistasis is when a gene at one location (locus) alters the phenotypic expression of a gene at another locus. Epistasis takes place when the action of one gene is modified by one or several other genes. These genes are sometimes called modifier genes. The gene whose phenotype is expressed is said to be epistatic, while the phenotype that is altered is said to be hypostatic. Sometimes hypostatic phenotypes are completely suppressed. Epistatic genes are not dominant over the genes they alter or suppress. Dominance refers to an interaction between alleles of the same gene, not different genes.

Examples of epistasis can be seen at both the genomic level and the phenotypic level. At the genomic level, it is highly possible that under certain conditions one gene could code for a protein that prevents transcription of the other gene. At the phenotypic level, examples include the gene causing albinism hiding the gene controlling the color of a person's hair. In another example, a gene coding for a widow's peak would be hidden by a gene causing baldness.

MUTATION:A. CHROMOSOMAL ABERRATION B. GENE MUTATION; HARMFUL AND BENIFICIAL EFFECT OF MUTATION

MUTATION

In biology, a mutation is an alteration in the nucleotide sequence of the genome of an organism, virus, or extrachromosomal DNA.Viral genomes contain either DNA or RNA. Mutations result from errors during DNA or viral replication, mitosis, or meiosis or other types of damage to DNA (such as pyrimidine dimers caused by exposure to ultraviolet radiation), which then may undergo error-prone repair (especially microhomology-mediated end joining), cause an error during other forms of repair, or cause an error during replication (translesion synthesis). Mutations may also result from insertion or deletion of segments of DNA due to mobile genetic elements

Mutations may or may not produce discernible changes in the observable characteristics (phenotype) of an organism. Mutations play a part in both normal and abnormal biological processes including: evolution, cancer, and the development of the immune system, including junctional diversity. Mutation is the ultimate source of all genetic variation, providing the raw material on which evolutionary forces such as natural selection can act.

Causes

Mutagenesis

Four classes of mutations are (1) spontaneous mutations (molecular decay), (2) mutations due to error-prone replication bypass of naturally occurring DNA damage (also called error-prone translesion synthesis), (3) errors introduced during DNA repair, and (4) induced mutations caused by mutagens. Scientists may also deliberately introduce mutant sequences through DNA manipulation for the sake of scientific experimentation.

One 2017 study claimed that 66% of cancer-causing mutations are random, 29% are due to the environment (the studied population spanned 69 countries), and 5% are inherited.

Humans on average pass 60 new mutations to their children but fathers pass more mutations depending on their age with every year adding two new mutations to a child.

Spontaneous mutation

Spontaneous mutations occur with non-zero probability even given a healthy, uncontaminated cell. Naturally occurring oxidative DNA damage is estimated to occur 10,000 times per cell per day in humans and 100,000 times per cell per day in rats.[31] Spontaneous mutations can be characterized by the specific change:

Tautomerism – A base is changed by the repositioning of a hydrogen atom, altering the hydrogen bonding pattern of that base, resulting in incorrect base pairing during replication.
Depurination – Loss of a purine base (A or G) to form an apurinic site (AP site).

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Deamination – Hydrolysis changes a normal base to an atypical base containing a keto group in place of the original amine group. Examples include C → U and A → HX (hypoxanthine), which can be corrected by DNA repair mechanisms; and 5MeC (5-methylcytosine) → T, which is less likely to be detected as a mutation because thymine is a normal DNA base.

Slipped strand mispairing – Denaturation of the new strand from the template during replication, followed by renaturation in a different spot ("slipping"). This can lead to insertions or deletions

Error-prone replication bypass

There is increasing evidence that the majority of spontaneously arising mutations are due to error-prone replication (translesion synthesis) past DNA damage in the template strand. In mice, the majority of mutations are caused by translesion synthesis. Likewise, in yeast, Kunz et al. found that more than 60% of the spontaneous single base pair substitutions and deletions were caused by translesion synthesis.

Errors introduced during DNA repair

See also: DNA damage (naturally occurring) and DNA repair

Although naturally occurring double-strand breaks occur at a relatively low frequency in DNA, their repair often causes mutation. Non-homologous end joining (NHEJ) is a major pathway for repairing double-strand breaks. NHEJ involves removal of a few nucleotides to allow somewhat inaccurate alignment of the two ends for rejoining followed by addition of nucleotides to fill in gaps. As a consequence, NHEJ often introduces mutations.

Induced mutation

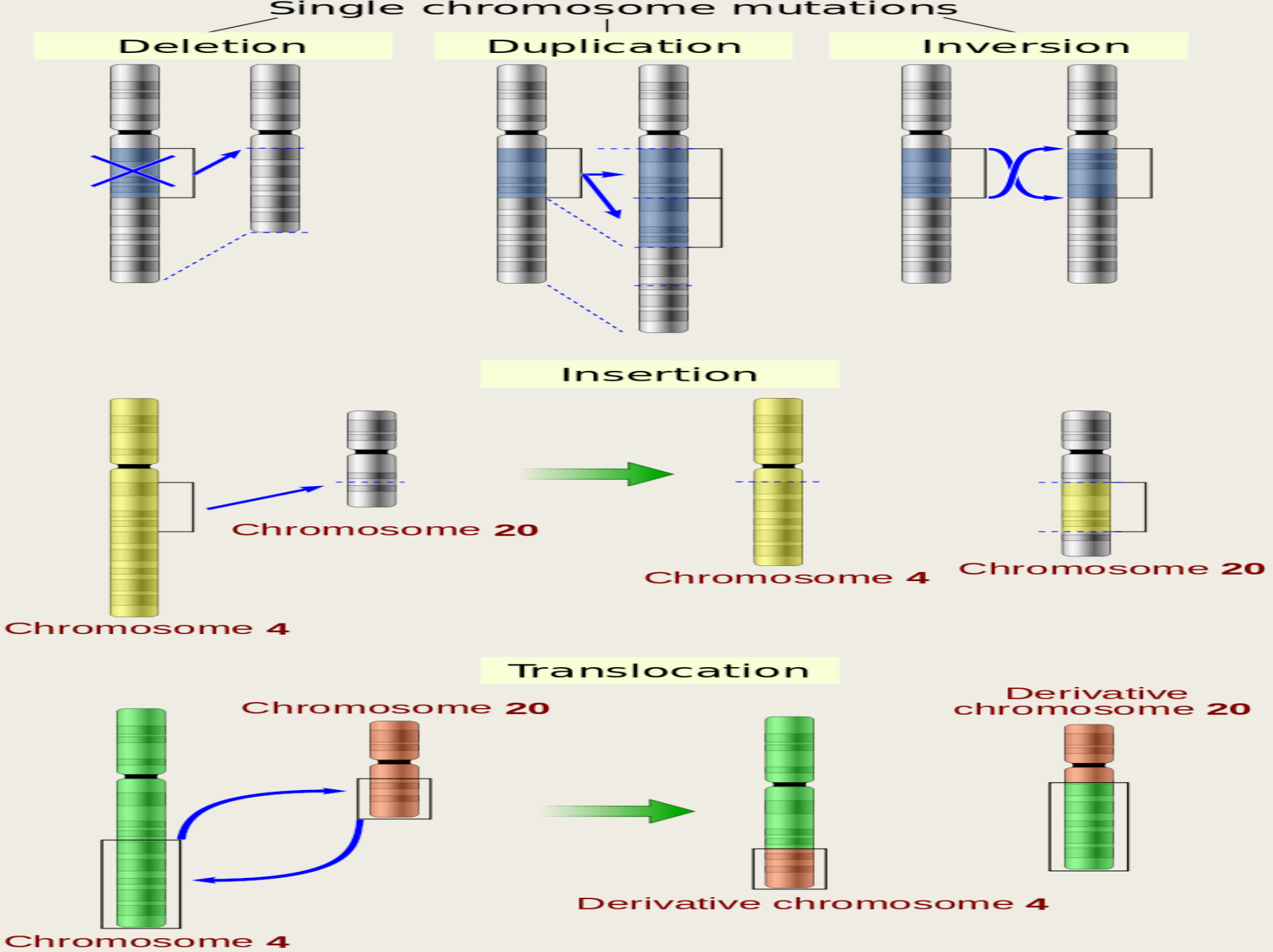
Induced mutations are alterations in the gene after it has come in contact with mutagens and environmental causes.

Induced mutations on the molecular level can be caused by:

Chemicals
Hydroxylamine
Base analogs (e.g., Bromodeoxyuridine (BrdU))
Alkylating agents (e.g., N-ethyl-N-nitrosourea (ENU). These agents can mutate both replicating and non-replicating DNA. In contrast, a base analog can mutate the DNA only when the analog is incorporated in replicating the DNA. Each of these classes of chemical mutagens has certain effects that then lead to transitions, transversions, or deletions.

Agents that form DNA adducts (e.g., ochratoxin A)
DNA intercalating agents (e.g., ethidium bromide)
DNA crosslinkers
Oxidative damage
Nitrous acid converts amine groups on A and C to diazo groups, altering their hydrogen bonding patterns, which leads to incorrect base pairing during replication.
Radiation
Ultraviolet light (UV) (non-ionizing radiation). Two nucleotide bases in DNA—cytosine and thymine—are most vulnerable to radiation that can change their properties. UV light can induce adjacent pyrimidine bases in a DNA strand to become covalently joined as a pyrimidine dimer. UV radiation, in particular longer-wave UVA, can also cause oxidative damage to DNA.
Ionizing radiation. Exposure to ionizing radiation, such as gamma radiation, can result in mutation, possibly resulting in cancer or death.

Whereas in former times mutations were assumed to occur by chance, or induced by mutagens, molecular mechanisms of mutation have been discovered in bacteria and across the tree of life. As S. Rosenberg states, "These mechanisms reveal a picture of highly regulated mutagenesis, up-regulated temporally by stress responses and activated when cells/organisms are maladapted to their environments—when stressed—potentially accelerating adaptation." Since they are self-induced mutagenic mechanisms that increase the adaptation rate of organisms, they have some times been named as adaptive mutagenesis mechanisms, and include the SOS response in bacteria, ectopic intrachromosomal recombination and other chromosomal events such as duplications.



Five types of chromosomal mutations

Classification of types
By effect on structure

Selection of disease-causing mutations, in a standard table of the genetic code of amino acids

The sequence of a gene can be altered in a number of ways.

Gene mutations have varying effects on health depending on where they occur and whether they alter the function of essential proteins. Mutations in the structure of genes can be classified into several types.

Large-scale mutations:Chromosome abnormality

Large-scale mutations in chromosomal structure include: Amplifications (or gene duplications) or repetition of a chromosomal segment or presence of extra piece of a chromosome broken piece of a chromosome may become attached to a homologous or non-homologous chromosome so that some of the genes are present in more than two doses leading to multiple copies of all chromosomal regions, increasing the dosage of the genes located within them.

Deletions of large chromosomal regions, leading to loss of the genes within those regions.

Mutations whose effect is to juxtapose previously separate pieces of DNA, potentially bringing together separate genes to form functionally distinct fusion genes (e.g., bcr-abl).

Large scale changes to the structure of chromosomes called **chromosomal rearrangement** that can lead to a decrease of fitness but also to speciation in isolated, inbred populations. These include:

Chromosomal translocations: interchange of genetic parts from nonhomologous chromosomes.

Chromosomal inversions: reversing the orientation of a chromosomal segment.

Non-homologous chromosomal crossover.

Interstitial deletions: an intra-chromosomal deletion that removes a segment of DNA from a single chromosome, thereby apposing previously distant genes. For example, cells isolated from a human astrocytoma, a type of brain tumor, were found to have a chromosomal deletion removing sequences between the Fused in Glioblastoma (FIG) gene and the receptor tyrosine kinase (ROS), producing a fusion protein (FIG-ROS). The abnormal FIG-ROS fusion protein has constitutively active kinase activity that causes oncogenic transformation (a transformation from normal cells to cancer cells).

Loss of heterozygosity: loss of one allele, either by a deletion or a genetic recombination event, in an organism that previously had two different alleles

2.Small-scale mutations: Small-scale mutations affect a gene in one or a few nucleotides. (If only a single nucleotide is affected, they are called point mutations.)
Small-scale mutations include:

Insertions add one or more extra nucleotides into the DNA. They are usually caused by transposable elements, or errors during replication of repeating elements. Insertions in the coding region of a gene may alter splicing of the mRNA (splice site mutation), or cause a shift in the reading frame (frameshift), both of which can significantly alter the gene product. Insertions can be reversed by excision of the transposable element.
Deletions remove one or more nucleotides from the DNA

Deletions remove one or more nucleotides from the DNA

. Like insertions, these mutations can alter the reading frame of the gene. In general, they are irreversible: Though exactly the same sequence might, in theory, be restored by an insertion, transposable elements able to revert a very short deletion (say 1–2 bases) in any location either are highly unlikely to exist or do not exist at all.

Substitution mutations, often caused by chemicals or malfunction of DNA replication, exchange a single nucleotide for another.These changes are classified as transitions or transversions.Most common is the transition that exchanges a purine for a purine (A ↔ G) or a pyrimidine for a pyrimidine, (C ↔ T). A transition can be caused by nitrous acid, base mispairing, or mutagenic base analogs such as BrdU. Less common is a transversion, which exchanges a purine for a pyrimidine or a pyrimidine for a purine (C/T ↔ A/G). An example of a transversion is the conversion of adenine (A) into a cytosine (C).

Point mutations are modifications of single base pairs of DNA or other small base pairs within a gene. A point mutation can be reversed by another point mutation, in which the nucleotide is changed back to its original state (true reversion) or by second-site reversion (a complementary mutation elsewhere that results in regained gene functionality). As discussed below, point mutations that occur within the protein coding region of a gene may be classified as synonymous or nonsynonymous substitutions, the latter of which in turn can be divided into missense or nonsense mutations.

CHROMOSOMAL ABERRATION

CHROMOSOMAL ABERRATION

Chromosome aberrations include changes in chromosome number (gains and losses) and changes in structure (deletions, inversions, and exchanges). Chromosomes can be viewed by standard light microscopy and many of these aberration types can be observed

A chromosomal disorder, chromosomal anomaly, chromosomal aberration, or chromosomal mutation is a missing, extra, or irregular portion of chromosomal DNA.

It can be from a typical number of chromosomes or a structural abnormality in one or more chromosomes. Chromosome mutation was formerly used in a strict sense to mean a change in a chromosomal segment, involving more than one gene

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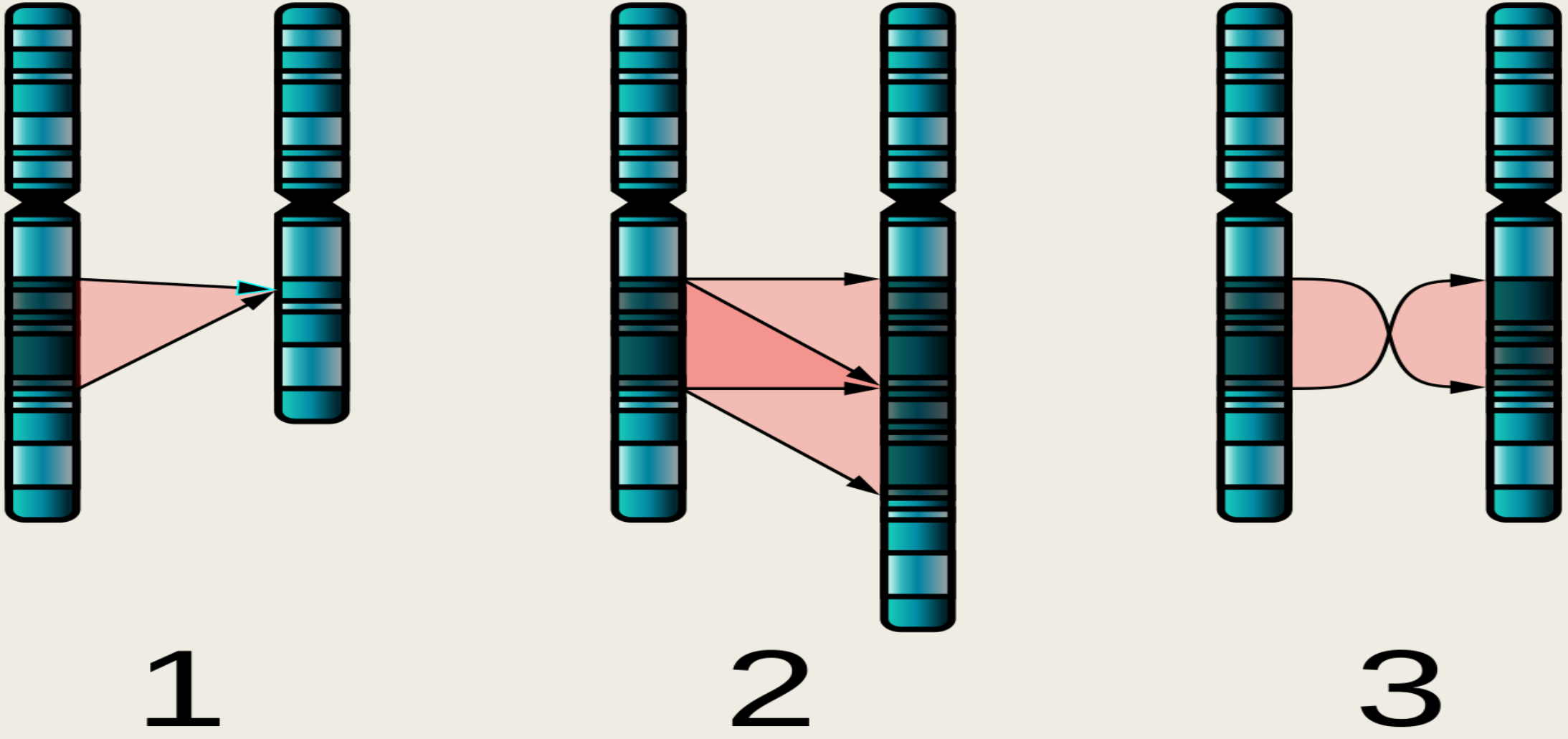
The term "karyotype" refers to the full set of chromosomes from an individual; this can be compared to a "normal" karyotype for the species via genetic testing. A chromosome anomaly may be detected or confirmed in this manner. Chromosome anomalies usually occur when there is an error in cell division following meiosis or mitosis. There are many types of chromosome anomalies. They can be organized into two basic groups, numerical and structural anomalies



The three major single-chromosome mutations: deletion (1), duplication (2) and inversion (3).

Numerical abnormality

This is called aneuploidy (an abnormal number of chromosomes), and occurs when an individual either is missing a chromosome from a pair (monosomy) or has more than two chromosomes of a pair (trisomy, tetrasomy, etc.).

An example of trisomy in humans is Down syndrome, which is a developmental disorder caused by an extra copy of chromosome 21; the disorder is therefore also called trisomy 21

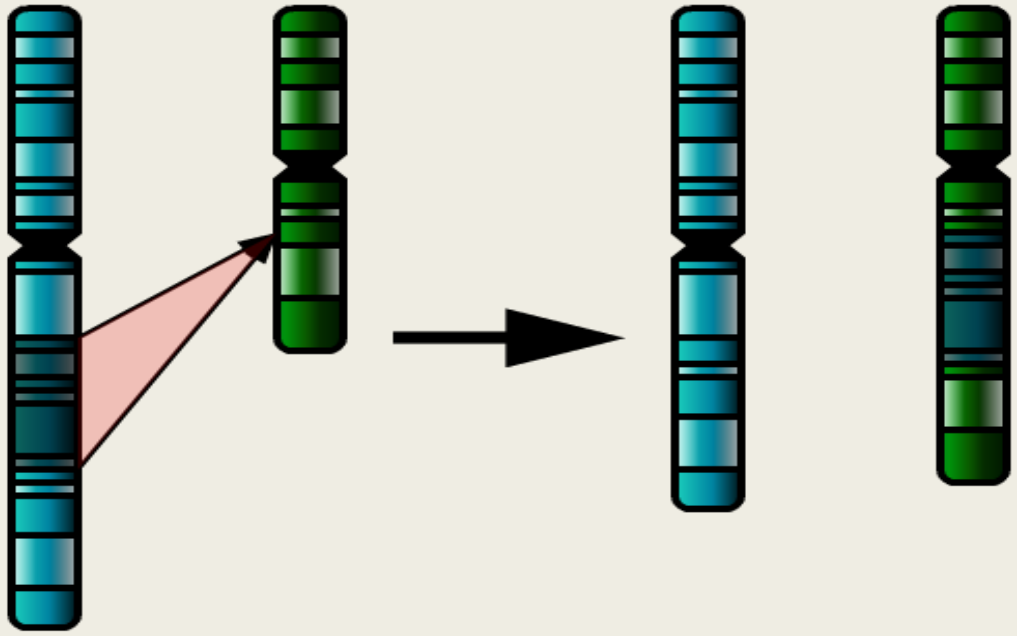
An example of monosomy is Turner syndrome, where the individual is born with only one sex chromosome, an X

Having an extra copy of this chromosome means that individuals have three copies of each of its genes instead of two, making it difficult for cells to properly control how much protein is made. Producing too much or too little protein can have serious consequences. Genes on chromosome 21 that specifically contribute to the various symptoms of Down syndrome are now being identified. The frequency of Trisomy 21 has been determined to be a function of advanced maternal age.

An example of monosomy is Turner syndrome, where the individual is born with only one sex chromosome, an X

Sperm aneuploidy

Exposure of male to certain lifestyle, environmental and/or occupational hazards may increase the risk of aneuploid spermatozoa. In particular, risk of aneuploidy is increased by tobacco smoking,and occupational exposure to benzene, insecticides, and perfluorinated compounds Increased aneuploidy is often associated with increased DNA damage in spermatozoa.



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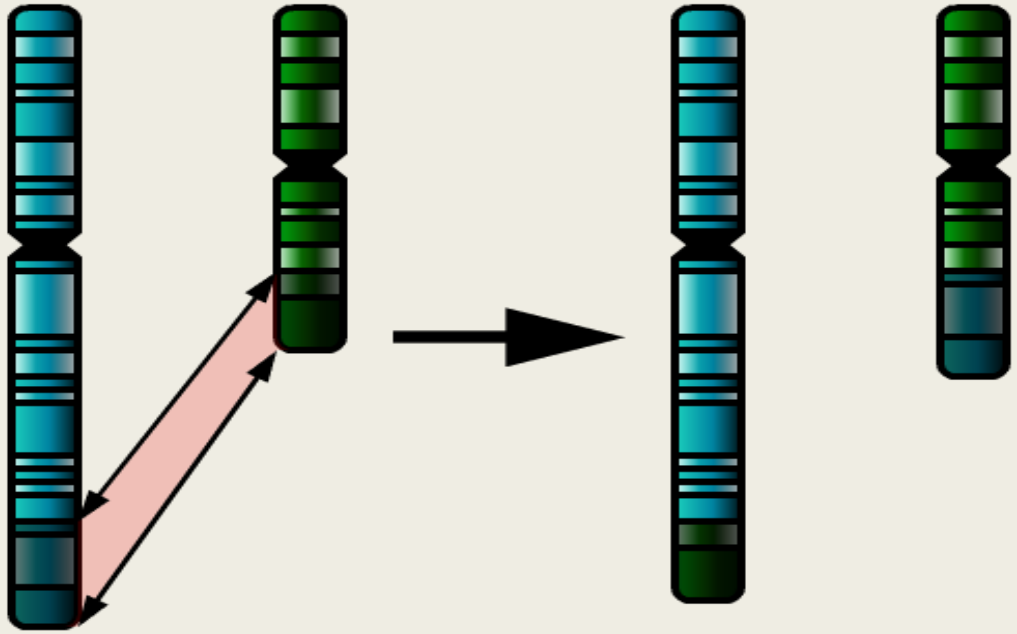

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The two major two-chromosome mutations: insertion (1) and Translocation (2).

Structural abnormalities:When the chromosome's structure is altered, this can take several forms

- Deletions: A portion of the chromosome is missing or deleted. Known disorders in humans include Wolf-Hirschhorn syndrome, which is caused by partial deletion of the short arm of chromosome 4; and Jacobsen syndrome, also called the terminal 11q deletion disorder.
- Duplications: A portion of the chromosome is duplicated, resulting in extra genetic material. Known human disorders include Charcot-Marie-Tooth disease type 1A, which may be caused by duplication of the gene encoding peripheral myelin protein 22 (PMP22) on chromosome 17.
- Translocations: A portion of one chromosome is transferred to another chromosome. There are two main types of translocations:
- Reciprocal translocation: Segments from two different chromosomes have been exchanged.

- Robertsonian translocation: An entire chromosome has attached to another at the centromere - in humans these only occur with chromosomes 13, 14, 15, 21, and 22.
- Inversions: A portion of the chromosome has broken off, turned upside down, and reattached, therefore the genetic material is inverted.
- Insertions: A portion of one chromosome has been deleted from its normal place and inserted into another chromosome.

- Rings: A portion of a chromosome has broken off and formed a circle or ring. This can happen with or without loss of genetic material.
- Isochromosome: Formed by the mirror image copy of a chromosome segment including the centromere.
- Chromosome instability syndromes are a group of disorders characterized by chromosomal instability and breakage. They often lead to an increased tendency to develop certain types of malignancies

Inheritance

Most chromosome abnormalities occur as an accident in the egg cell or sperm, and therefore the anomaly is present in every cell of the body. Some anomalies, however, can happen after conception, resulting in Mosaicism (where some cells have the anomaly and some do not). Chromosome anomalies can be inherited from a parent or be "de novo". This is why chromosome studies are often performed on parents when a child is found to have an anomaly. If the parents do not possess the abnormality it was not initially inherited; however it may be transmitted to subsequent generations.

Acquired chromosome abnormalities

Most cancers, if not all, could cause chromosome abnormalities with either the formation of hybrid genes and fusion proteins, deregulation of genes and overexpression of proteins, or loss of tumor suppressor genes (see the "Mitelman Database" and the Atlas of Genetics and Cytogenetics in Oncology and Haematology,. Furthermore, certain consistent chromosomal abnormalities can turn normal cells into a leukemic cell such as the translocation of a gene, resulting in its inappropriate expression

DNA damage during spermatogenesis

During the mitotic and meiotic cell divisions of mammalian gametogenesis, DNA repair is effective at removing DNA damages. However, in spermatogenesis the ability to repair DNA damages decreases substantially in the latter part of the process as haploid spermatids undergo major nuclear chromatin remodeling into highly compacted sperm nuclei. As reviewed by Marchetti et al., the last few weeks of sperm development before fertilization are highly susceptible to the accumulation of sperm DNA damage. Such sperm DNA damage can be transmitted unrepaired into the egg where it is subject to removal by the maternal repair machinery. However, errors in maternal DNA repair of sperm DNA damage can result in zygotes with chromosomal structural aberrations.

Melphalan is a bifunctional alkylating agent frequently used in chemotherapy. Meiotic inter-strand DNA damages caused by melphalan can escape paternal repair and cause chromosomal aberrations in the zygote by maternal misrepair. Thus both pre- and post-fertilization DNA repair appear to be important in avoiding chromosome abnormalities and assuring the genome integrity of the conceptus

What is a gene mutation and how do mutations occur?

A gene mutation is a permanent alteration in the DNA sequence that makes up a gene, such that the sequence differs from what is found in most people. Mutations range in size; they can affect anywhere from a single DNA building block (base pair) to a large segment of a chromosome that includes multiple genes.

Gene mutations can be classified in two major ways: Hereditary mutations are inherited from a parent and are present throughout a person's life in virtually every cell in the body. These mutations are also called germline mutations because they are present in the parent's egg or sperm cells, which are also called germ cells. When an egg and a sperm cell unite, the resulting fertilized egg cell receives DNA from both parents. If this DNA has a mutation, the child that grows from the fertilized egg will have the mutation in each of his or her cells.

Acquired (or somatic) mutations occur at some time during a person's life and are present only in certain cells, not in every cell in the body. These changes can be caused by environmental factors such as ultraviolet radiation from the sun, or can occur if an error is made as DNA copies itself during cell division. Acquired mutations in somatic cells (cells other than sperm and egg cells) cannot be passed to the next generation.

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Somatic mutations that happen in a single cell early in embryonic development can lead to a situation called mosaicism. These genetic changes are not present in a parent's egg or sperm cells, or in the fertilized egg, but happen a bit later when the embryo includes several cells. As all the cells divide during growth and development, cells that arise from the cell with the altered gene will have the mutation, while other cells will not. Depending on the mutation and how many cells are affected, mosaicism may or may not cause health problems.

HARMFUL and BENEFICIAL EFFECT OF MUTATION

Disease causation

Changes in DNA caused by mutation in a coding region of DNA can cause errors in protein sequence that may result in partially or completely non-functional proteins. Each cell, in order to function correctly, depends on thousands of proteins to function in the right places at the right times. When a mutation alters a protein that plays a critical role in the body, a medical condition can result.

One study on the comparison of genes between different species of Drosophila suggests that if a mutation does change a protein, the mutation will most likely be harmful, with an estimated 70 percent of amino acid polymorphisms having damaging effects, and the remainder being either neutral or weakly beneficial. Some mutations alter a gene's DNA base sequence but do not change the protein made by the gene. Studies have shown that only 7% of point mutations in noncoding DNA of yeast are deleterious and 12% in coding DNA are deleterious. The rest of the mutations are either neutral or slightly beneficial.

Inherited disorders: Genetic disorder

If a mutation is present in a germ cell, it can give rise to offspring that carries the mutation in all of its cells. This is the case in hereditary diseases. In particular, if there is a mutation in a DNA repair gene within a germ cell, humans carrying such germline mutations may have an increased risk of cancer. A list of 34 such germline mutations is given in the article DNA repair-deficiency disorder. An example of one is albinism, a mutation that occurs in the OCA1 or OCA2 gene. Individuals with this disorder are

DNA damage can cause an error when the DNA is replicated, and this error of replication can cause a gene mutation that, in turn, could cause a genetic disorder. DNA damages are repaired by the DNA repair system of the cell. Each cell has a number of pathways through which enzymes recognize and repair damages in DNA. Because DNA can be damaged in many ways, the process of DNA repair is an important way in which the body protects itself from disease. Once DNA damage has given rise to a mutation, the mutation cannot be repaired.

Role in carcinogenesis

On the other hand, a mutation may occur in a somatic cell of an organism. Such mutations will be present in all descendants of this cell within the same organism. The accumulation of certain mutations over generations of somatic cells is part of cause of malignant transformation, from normal cell to cancer cell.
Cells with heterozygous loss-of-function mutations (one good copy of gene and one mutated copy) may function normally with the unmutated copy until the good copy has been spontaneously somatically mutated. This kind of mutation happens often in living organisms, but it is difficult to measure the rate. Measuring this rate is important in predicting the rate at which people may develop cancer

Point mutations may arise from spontaneous mutations that occur during DNA replication. The rate of mutation may be increased by mutagens. Mutagens can be physical, such as radiation from UV rays, X-rays or extreme heat, or chemical (molecules that misplace base pairs or disrupt the helical shape of DNA). Mutagens associated with cancers are often studied to learn about cancer and its prevention.

Prion mutations

Prions are proteins and do not contain genetic material. However, prion replication has been shown to be subject to mutation and natural selection just like other forms of replication. The human gene PRNP codes for the major prion protein, PrP, and is subject to mutations that can give rise to disease-causing prions.

Beneficial mutations

Although mutations that cause changes in protein sequences can be harmful to an organism, on occasions the effect may be positive in a given environment. In this case, the mutation may enable the mutant organism to withstand particular environmental stresses better than wild-type organisms, or reproduce more quickly. In these cases a mutation will tend to become more common in a population through natural selection. Examples include the following:

HIV resistance: a specific 32 base pair deletion in human CCR5 (CCR5-Δ32) confers HIV resistance to homozygotes and delays AIDS onset in heterozygotes.[

Malaria resistance: An example of a harmful mutation is sickle-cell disease, a blood disorder in which the body produces an abnormal type of the oxygen-carrying substance hemoglobin in the red blood cells.

One-third of all indigenous inhabitants of Sub-Saharan Africa carry the allele, because, in areas where malaria is common, there is a survival value in carrying only a single sickle-cell allele (sickle cell trait).Those with only one of the two alleles of the sickle-cell disease are more resistant to malaria, since the infestation of the malaria Plasmodium is halted by the sickling of the cells that it infests

Antibiotic resistance: Practically all bacteria develop antibiotic resistance when exposed to antibiotics. In fact, bacterial populations already have such mutations that get selected under antibiotic selection.

Obviously, such mutations are only beneficial for the bacteria but not for those infected.

Lactase persistence. A mutation allowed humans to express the enzyme lactase after they are naturally weaned from breast milk, allowing adults to digest lactose, which is likely one of the most beneficial mutations in recent human evolution

THANK YOU