10. LINKAGE

10.1 Chromosome is the unit of transmission of genetic information during meiosis. Most chromosomes contain a large number of genes and those that are located on the same chromosome are said to be **linked.** During gamete formation, the homologous pairs of chromosomes undergo a reciprocal exchange of chromosome segments, resulting in recombination of the alleles present on the homologues. In case of genes that show complete dominance, **coupling** and **repulsion** determine the types of parental gametes produced after meiosis.

Coupling – Coupling refers to the case where dominant alleles of autosomal genes (A, B) (Fig) are on the same homologue chromosome and both of their recessive alleles (a, b) are on the other homologue chromosome, thus producing the parental gametes AB and ab. They are also referred to as cis.

Repulsion – Repulsion refers to the case where each homologue chromosome has one dominant and one recessive allele from the two genes, thus, the parental gametes produced are Ab and aB (Fig). They are also called trans.

Linkage – Linkage is the tendency of the alleles that are located in linear sequence at close proximity on a chromosome to be inherited together during gamete formation. It was first reported by Sutton and Boveri (1902-1903) as they proposed the "Chromosomal theory of inheritance".

Strength of linkage between two gene loci is inversely proportional to the distance between them on the chromosome, called **interlocus distance.** Two randomly selected genes can be so close to each other, that there is hardly any chance of crossing over between them during meiosis, thus producing Parental or NCO (Non-crossover) gametes. This type of linkage is called **complete linkage.** As the distance between two gene loci increases, the occurrence of crossing over becomes more probable, leading to increased proportion of recombinant gametes. Thus, crossing over between two linked genes results in **incomplete linkage**. How far the distance between the two loci may be, the number of CO or recombinant gametes should not exceed 50% of the total number of gametes produced, as in **Fig.** a, both A and B are located on the single pair of homologs; crossing-over between the sister chromatids produces parental gametes (AB and ab), while, crossover between the non-sister chromatids results in formation of Ab and aB, the recombinant gametes. Thus, the ratio between AB: Ab: aB: ab is always 1:1:1:1.

Linkage group – All genes located on a single chromosome form a linkage group. During cell division, they move together as a unit and are inherited as a single group. There is one linkage group for each chromosome, thus, corresponds to the haploid number of chromosomes in an individual.

10.2 Detection of crossing over

In 1911, T.H. Morgan coined the term 'crossing-over' to describe the physical exchange leading to recombination. In course of his study on *Drosophila* mutants, he postulated that chiasmata could represent the point of exchange of genes between two homologous chromosomes. Since the possibility of chiasma formation is less likely between two genes located relatively close to each other, the probability of recombination is low between them and vice versa.

In 1930s, H. Creighton and B. McClintock choose two linked genes on chromosome 9 of *Zea mays* to study the relationship between chiasmata and crossing over. At one locus, the alleles colourless (c) and coloured (C) control the colour of endosperm **(Fig)**; at the other locus, starchy (Wx) and waxy (wx) the loci. Reason behind its choice was one of the homologs contains two unique cytological markers, a densely stained knob at one end of the chromosome and a translocated piece of chromosome 8 at the other end. This plant was crossed to one that was homozygous for the colourless allele (cc) and heterozygous for the waxy/starchy allele (Wx/wx). Amongst the offspring with various phenotypes, the colourless waxy ones were found to bear the translocated segments, but the knob was absent **(Fig)**; this was obvious even if physical exchange occurred during crossing over. In contrast, the coloured starchy phenotype, which was the resultant of parental as well as recombinant gametes were found to bear only the knob, but not the translocated segment in some cases. Thus, it was detected that crossing over involves physical exchange of chromosomes.

10.3 Molecular mechanism of crossing over

The first plausible model to explain the mechanism of crossing over was formulated by Robin Holliday. According to **Holliday model (Fig)** DNA recombination can occur as a result of the single strand break and subsequent rejoining of heterologous DNA strands.

Two homologous double helices become so aligned that the 3'-5' strands of the sister chromatids face each other. An endonuclease nick is formed followed by strand displacement; the cleaved

ends leave their complementary strands of sister chromatids and undergo H-bonding with that of the non-sister ones, thus producing a **heteroduplex** DNA strand called **Holliday structure (Fig).** A cross bridge or branch is formed that can migrate along the heteroduplex, followed by duplex separation. Following 180^0 rotation, the **Chi form (Fig)** is resolved by cutting and ligating either the two exchanged strands or the originally unexchanged ones. The former generates a pair of parental duplexes, except for a stretch in the middle containing one strand from each parent, while the latter produces two duplexes that are recombinant.

Holliday model also postulates that the heteroduplex DNA mismatch can be repaired by an enzymatic correction system that recognizes mismatches and excises the mismatched base from one strand, replacing the excised base by synthesis of the appropriate complementary one using the remaining strand as a template. The resultant molecule would carry either wild type or mutant allele, depending on which one had been excised **(Fig from copy)**.

10.4 Gene mapping and three-point test cross

Gene mapping involves the technique used to construct a model of the linear sequence of genes of a particular chromosome by identifying the relative positions of the gene loci on the chromosome and calculating the distance between them. Unlike physical mapping, where distance is measured in terms of the number of base pairs, gene mapping technique is based on linkage information. The pre-requisites of this technique are specific genetic markers or traits that can be distinctly differentiated amongst the parents and a mapping population. Recombination frequency (θ) determines the frequency of a single cross-over between two genes during meiosis.

When single cross-over occurs between two non-sister chromatids the other two chromatids of the tetrad are not involved in the exchange and enter the gamete unchanged. Thus even if in 100% of the tetrads a single cross-over occurs between two linked genes, only 50% of the potential gametes will be recombinant. When two linked genes are more than 50 map units apart, a crossing over can theoretically be expected to occur between them in 100% of the tetrads and each tetrad will yield equal proportion of the four gametes.

However, in a single tetrad, two or more exchanges may occur between non-sister chromatids as a result of multiple crossing-over events. In case of double cross-overs (DCO) two independent

exchanges must occur simultaneously. Thus, to study DCO, at least three gene pairs must be investigated, each heterozygous for two alleles.

Product Law – The mathematical probability of two independent events occurring simultaneously is equal to the product of the individual probabilities. Suppose, in an experiment, 20% single crossover (SCO) gametes are recovered between A and B loci and 30% SCO are recovered between B and C loci. Here, the probability (*p*) of formation of SCO between A and B would be 20/100, *i.e.* 0.2 and that of B and C would be 30/100, *i.e.* 0.3. Whereas, the probability of recovering DCO gametes resulting from two simultaneous exchanges between A and B, B and C should be (0.2) (0.3) = 0.06 or 6%, which is much less than the expected frequency of each type of SCO gametes.

This frequency gets even lower as the map distance between the three genes decreases. If the distance between A and B is 2 map unit (mu) and that between B and C is 3 mu, the expected frequency of each type of SCO gamete would be 2% and 3% respectively. The probability of recovering DCO gametes would therefore, be (2/100) (3/100) = (0.02) (0.03) = 0.0006, *i.e.* only 6 events in 10,000, the frequency of occurrence being 0.06%. In this case, at least 10000 offspring are required to detect double crossover. Thus, it is evident that, if four or more genes are being mapped, even fewer triple or quadruple crosses can be expected to occur.

Three Point Test Cross – In order to execute a successful mapping cross between three or more linked genes, the following criteria must be met:

1. The genotype of the organism producing the crossover gametes must be heterozygous at all loci under consideration.
2. Genotypes of all gametes must be accurately expressed by the phenotypes of the offspring.
3. Sufficient number of offspring must be produced to recover the representative types of all crossover classes.

All these criteria are met when three X-linked recessive mutant genes of *Drosophila melanogaster*, *viz.* yellow body colour (*y*), white eye colour (*w*) and echinus eye shape (*ec*) are considered for the three-point mapping cross. It is primarily assumed that the three genes are located in successive order on X-chromosome. In P_1 generation, the males hemizygous for all

three wild-type genes (in male, the X-linked genes are hemizygous, since they lack any allelomorph on the Y chromosome) are crossed with the females homozygous for the three mutant alleles. Thus, in F_1 generation the resultant males being hemizygous for the mutant traits are yellow (*y*), white eyed (*w*) with echinus eye (*ec*), while the females being heterozygous at the three loci, are phenotypically wild type. Due to the genotypes of the parents (P_1), these heterozygous F_1 females carry the wild-type alleles on one homolog and the mutant ones on the other.

In the present cross, the gametes formed by F_1 males either carry an X chromosome bearing three mutant alleles or a Y chromosome that lack any of these gene loci. Hence, the phenotypic expression of the F_2 male and female offspring are determined by the non-crossover and crossover gametes produced by the heterozygous F_1 females, which however, can be identified by observing the F_2 phenotypes. After the cross, the F_2 offspring needs to be segregated on the basis of non-crossover and crossover categories. The NCO F_2 phenotypes are derived from the parental gametes formed of heterozygous F_1 females, which contain the X chromosomes unaffected by recombination during meiosis **(Fig.)**. Approximately equal proportion of two types of complementary gametes and subsequently their phenotypes called **reciprocal gametes and phenotypes** are expressed in F_2. These flies are either wild type or yellow, white-eyed and echinus consist maximum number of offspring in F_2 generation (94.44%) **(Fig.)**. The second category of offspring present in least number are formed by double-crossover gametes. This group represents two independent but simultaneous single crossover expressions like yellow, echinus but normal eye-colour and white-eye with normal body colour and eye shape. Together, these DCO phenotypes constitute only 0.06% of the F_2 offspring **(Fig.)**. The rest of the F_2 population are derived from two types of single crossover events, either between yellow body and white eye loci or between white eye and echinus eye loci. The former type of recombination results in 1.50% of F_2 flies having yellow body, normal eye colour and shape and white eyed, echinus flies with normal body colour. The rest 4% offspring represent the latter group of SCO gametes comprising of yellow body, white-eyed flies with normal eye shape and normal body coloured, normal eye coloured flies with echinus eyes **(Fig.)**.

Prior to construction of a gene map, it is important to determine the sequence of the loci on the chromosome. In the present experiment the possible arrangements would have either been *body*

colour, eye colour, eye shape or *eye colour, body colour, eye shape* or *body colour, eye shape, eye colour*. Thus the DCO gametes produced by the heterozygous F_1 females would have followed one of the following successions:

i. *y* w^+ *ec* and y^+ *w* ec^+

ii. *w* y^+ *ec* and w^+ *y* ec^+

iii. *y* ec^+ *w* and y^+ *ec* w^+

Upon crossing with the hemizygous F_1 male the first types of DCO gametes would have produced yellow bodied flies with normal eye colour but echinus shape and white eyed ones with normal eyes and body colour. The second set would have resulted in white and echinus eyed offspring with normal body colour as well as yellow flies with normal eye colour and shape. In case of the third set the offspring would have been yellow, white eyed with normal eye shape and echinus eyed with normal colour of body and eyes. Since in F_2 generation the DCO gametes yield the first set of phenotypes the sequence of gene loci must have been *body colour, eye colour, eye shape.*

The map distance between each two loci is equal to the percentage of all single as well as double crossover events occurred between them. Thus, the map distance between *y* and *w* is 1.5mu + 0.06 mu = 1.56 mu. Similarly, the distance between *w* and *ec* is 4mu + 0.06mu = 4.06mu, the sequence of the three loci being *y w* and *ec*.

10.5 Coefficient of coincidence and interference

Often in mapping experiments, the observed frequency of DCO is less than its expected number. The inhibition of further crossover events by a crossover at nearby region of the chromosome causes this reduction. Such inhibition is called **interference** (**I**) and the disparities caused by interference can be quantified by **coefficient of coincidence** (**C**)**.** The virtual ratio between the observed and expected frequency of DCO should always be 1, but physical constraints prevent the formation of closely placed chiasma along the chromosome and cause interference. Coefficient of coincidence indicates the actual proportion of double crossover

events to its anticipated value and its difference from the virtual ratio gives the extent of interference.

Thus, **C** = Observed DCO / Expected DCO

I = 1 - C

If interference is complete and no double crossovers occur, then I = 1. Interference can be positive or negative, depending on the number of the DCO; if the observed DCO exceeds its predicted value, then C >1 and I becomes negative, showing negative interference. In contrast, if the observed DCO is less than its expected value, C <1 and I becomes positive, indicating positive interference. In general, the closer the genes are located along the chromosome, the more positive interference would occur.

10.6 Utility of gene mapping

The essence of gene mapping is to place a collection of molecular markers onto their respective positions on the genome. It is important as it identify genes responsible for heritable diseases and different useful traits in plants and animals like disease resistance, yield etc. Thus, gene mapping uses the information from DNA to develop new ways to treat, cure or even prevent thousands of diseases. The Human Genome Project (HGP) was an international project to provide a complete and accurate sequence of the 03 billion DNA base pairs that make up the human genome and to find all the estimated 20,000 to 25,000 human genes. Crossing over is affected by distance between genes, distance from centromere, heterochromatin association, chromosomal aberration, genotype, sex, age of female and environmental factors. Various genetic map functions have been proposed to infer the unobservable genetic distance between two loci from the observable recombination fraction between them.

10.7 Problems on gene mapping

Type 1 – It is possible to develop a gene map, showing the order of the loci and the distance between them by observing the number of offspring showing recombinant phenotypes. A

standard problem is to determine the order of three loci known to be linked on one pair of the autosomes. Solution of the problem requires

i) a determination of the relative order of loci, and

ii) the map distances between loci.

A cross is made between homozygous wild-type female Drosophila (a+ a+ b+ b+ c+ c+) and triple-mutant males (aa bb cc) (the order here is arbitrary). The F1 (a+a b+b c+c) females are test crossed back to the triple-mutant males and the F2 phenotypic ratios are as follows: “a+ b c” 18, “a b+ c” 112, "a b c” 308, “a+ b+ c” 66, “a b c+” 59, “a+ b+ c+” 321, “a+ b c+” 102 “a b+ c+” 15 =1000

1. The gene order can be determined by examination of the relative frequency of the F2 phenotypes.

a). Linked loci tend to stay together, hence, the non-crossover (NCO) or parental phenotypes should be most frequent (and equal in number). In this case a+ b+ c+ (321) and a b c (308).

b). Simultaneous crossovers between the outside and middle loci are unlikely, hence, the double-crossover (DCO) genotypes should be the least frequent. We observe a+ b c (18) and a b+ c+ (15).

c). To determine the physical order of loci, we would compare the parental and double - crossover phenotypes. The marker that appears to “switch places” is in the middle. Here, the a+b+c+ NCO and a b+c+ DCO phenotypes indicate that the a locus falls between the b and c loci. The correct order of the loci is b a c (or c a b).

d). The coupling phase of the trihybrid F1 is b+ a+ c+ / b a c.

2. The remaining two pairs of phenotypes correspond to single-crossovers (SCO) events in the region between either b and a, or between a and c.

a). b+ a c (112) and b a+ c+ (102) phenotypes indicate crossovers between b & a.

b). b+ a+ c (66) and b a c+ (59) phenotypes indicate crossovers between c & a.

3. The percent recombination between two markers indicates the map distance between them: 1% recombination = 1 map unit (m.u.). To determine the map distance between a pair of loci, we would count the number of SCO and DCO events, and use the following formula:

Map distance = % recombination

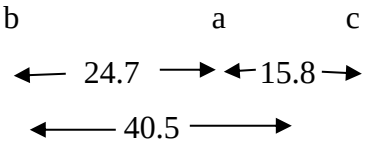
= (# in SCO phenotypes + # in DCO phenotypes x 100) ÷ (total # progeny)

(b⇔a) Map distance = {(112 + 102 + 18 + 15) x 100} ÷ 1000 = 24.7% = 24.7 m.u.

(a⇔c) Map distance = {(66 + 59 + 18 + 15) x 100} ÷ 1000 = 15.8% = 15.8 m.u.

(b⇔c) Map distance = (24.7 m.u. + 15.8 m.u.) = 40.5 m.u.

4. We can now draw a map segment showing order and distances among loci. Again, note that the orders b-a-c and c-a-b are equivalent and that the left/right the orientation of this map is arbitrary.



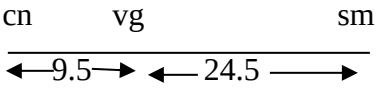
C.C. = (observed DCO) / (expected DCO)

= (33) / (0.247) (0.158) (1000) = 33 / 39 = 0.846

Interference = 1 - C.C. = 1 - 0.846 = 0.154 =15.4%.

Type 2 - The gene map can be used as a table of probabilities to predict the expected amount of recombination between certain loci. In a test cross the male contributes only recessive alleles. Recombination occurs in the formation of the female gametes. Therefore whatever alleles present in the female gamete will be expressed in the phenotype of the offspring. There is a certain probability that a cross-over will form between a and b loci (= map distance between a and b) and another independent probability that a cross-over will occur between b and c loci (= map distance between b and c). The probability of a double cross-over is the product of these two independent probabilities.

Given the map segment



In a test cross of cn+ vg+ sm+ // cn vg sm

Expected DCO = (% recomb. cn-vg) (% recomb. vg-sm)

= 0.095 x 0.245 = 2.3%

Therefore we expect to find 2.3% of the female gametes to be the results of double crossovers

1.15% cn+ vg sm+

1.15% cn vg+ sm

Expected SCO (cn-vg)

From the gene map 9.5% of the gametes would be expected to have crossovers between cn and vg, however this includes the 2.3% of double crossovers.

Therefore 9.5 -2.3 = 7.2% of the female gametes should have single crossovers:

3.6% cn vg+ sm+ &. 3.6% cn+ vg sm

Expected SCO (vg-sm)

From the gene map 24.5% of the gametes would be expected to have crossovers between vg and sm, this includes the 2.3% of double crossovers. Therefore 22.2% of the female gametes should have single crossovers

11.1% cn+ vg+ sm & 11.1% cn vg sm+

Total crossovers = 2.3% + 7.2% + 22.2% = 31.7%

Expected 68.3% parental gametes (34.15% of each).

Female gametes =

34.15 % cn+ vg+ sm+

34.15 % cn vg sm

11.1 % cn vg sm+

11.1 % cn+ vg+ sm

3.6 % cn vg+ sm+

3.6 % cn+ vg sm

1.15% cn vg+ sm

1.15 % cn+ vg sm+

Male gametes = 100 % cn vg sm

These percentages can then be used to determine an expected ratio.

wild-type : cn vg sm : cn vg : sm : cn : vg sm : vg : cn sm

34.15 : 34.15 : 11.1 :11.1:3.6 : 3.6 : 1.15 : 1.15

29.7 : 29.70 : 9.7 : 9.7 :3.1 : 3.1 : 1 : 1

In the region cn-sm 2.3% double crossover type were expected. However if the C.C. is known to be 70% for this region, then the number of expected double crossovers is modified (0.7 x 2.3) = 1.61% and the number of other expected phenotypes are modified accordingly.

Problem 1

A cross was made between purple leaf (p), glossy seedling (g), dwarf variety (t) and wild type. F1 plants were test crossed and the following proportions were obtained when a sample of 1000 plants were counted.

Wild type (P G T)	475
p g t	469
p G T	8
P g t	7
p G t	18
P g T	23
P G t	0
p g T	0

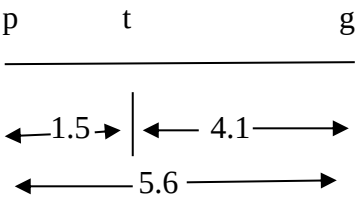
Determine the order of 3 genes and prepare a chromosome map. Find out the coefficient of coincidence.

Recombination percentage between p - g = {(8+7+18+23) x 100} ÷ 1000 = 5.6%

Recombination percentage between p – t = {(8 +7+0+0) x 100} ÷ 1000 = 1.5%

Recombination percentage between t – g = {(18 + 23 + 0 + 0) x 100} ÷ 1000 = 4.1%

The recombination value between p and g (5.6%) is equal to (p – t) + (t – g) = (1.5+4.1) % = 5.6%. Therefore, t should be located between p and g; thus the order of three genes on the chromosome is p t g / P T G. The map distances are:



Since the actual DCO is 0 in the population the coefficient of coincidence is 0.

Problem 2.

We have a portion of a chromosome map reading a 10 b 20 d

Out of 1000 individuals in a progeny, what proportions of phenotypes would be expected after the test cross? (co-efficient of coincidence = 0.5).

Expected DCO between a – d would be 10% of 20% = 2%

Actual DCO = 0.5 x 2 = 1%

Therefore, out of 1000 offspring, DCO are 10.

Recombination percentage between a – b = 10% = {(SCO (a – b) + 10) x 100} ÷ 1000

Or SCO (a- b) = 100-10 = 90 offspring.

Recombination percentage between b – c = 20% = {(SCO (b –c) + 10) x 100} ÷ 1000

Or SCO (b –c) = 200 – 10 = 190 offspring

Parental combinations = {1000 – (190 + 90 +10)} = 710 offspring.

A B D and a b d: Parental combinations = 710 offspring.

A b d and a B D: SCO (a – b) = 90 offspring

A B d and a b D: SCO (b – d) = 190 offspring

A b D and a B d: DCO (a – d) = 10 offspring

10.9 Sex-Linked Inheritance

Traits can be either **Autosomal** (genes are located on the non-sex chromosomes) or **Sex-linked** (genes are located on the sex chromosomes). Sex chromosomes, designated as **X** and **Y** determine gender of the offspring; **XX** genotype for female and **XY** for male.

Y-linked inheritance - Males being the possessors of Y chromosome, are the only carriers of **Y-linked traits**, all of which are transmitted from father to son and thus expressed. Approximately three dozen Y-linked traits have yet been discovered, of which, ZFY, H-YA, AZF2, TSPY, SRY etc. are some most important ones **(Fig. pedigree for Y-linked trait).**

X-linked inheritance - The first evidence of **X-linked trait** was reported by T.H. Morgan (1910) during his studies of the white eye mutation in *Drosophila* **(Fig)**. The normal wild-type red eye colour is dominant to white eye-colour. Unlike typical Mendalian monohybrid cross, reciprocal crosses between red-eyed and white-eyed flies did not yield identical result. This led Morgan to conclude that the white locus is present on the X-chromosome rather than on one of the autosomes. He hypothesized that the recessive allele for white-eye is present on X-chromosome but absent on Y. Females thus have two available gene loci, one on each X- chromosome; whereas males have only one available locus on the single X. A crisscross pattern occurs in X-linked recessive inheritance because females exhibiting a recessive trait must contain the mutant allele on both X-

chromosomes. Since male offspring receive one of their mother's two X-chromosomes and are hemizygous for all alleles present on that X, all sons will express the same recessive X-linked traits as their mother.

There are about 1,098 human X-linked genes, some of which code for various abnormalities like hemophilia (A and B), Duchenne muscular dystrophy, fragile-X syndrome, high blood pressure, congenital night blindness, G6PD deficiency, colour blindness for red and green light, hypophosphatemic rickets, Alport syndrome, Hunter syndrome, ichthyosis, Lesch-Nyhan syndrome, diabetes insipidus etc. These X-linked traits can be easily identified in a pedigree, because of the crisscross pattern of inheritance **(Fig. pedigree for human colour blindness).** The mother in generation passes the trait on to her son, but not to her daughters. If the offspring in generation II have children by normal individual, the diseased sons will produce all normal males and female offspring. The normal daughters in turn, will produce normal female offspring as well as diseased and normal male offspring. Unusual circumstance may be associated with X-linked disorders; if an X-linked disorder is lethal to the affected individual prior to reproductive maturation, the disorder is manifested exclusively in males. This is because almost the only sources of lethal allele in the population are heterozygous females, who are carriers but do not express the disorder. They pass the allele to one half of their sons, who develop the disease as they are hemizygous. Heterozygous females also pass the allele to one half of their daughters, who become carriers but do not develop the disorder **(Fig for Lesch-Nyhan syndrome).**

X-linked recessive inheritance

- Males are more likely to be affected because they only need one copy of the mutant allele to express the phenotype.
- All of the daughters of the affected males are obligate carriers.
- Sons of the heterozygous females have 50% chance of receiving the mutant allele and from an affected grandfather 50% of his grandsons receive these disorders.

Manifesting Heterozygous – When a female carrier of a recessive X-linked allele has phenotypic expression of a disease, she is referred to as a Manifesting Heterozygous.

X-linked dominant inheritance

- A single dominant allele on the X chromosome can lead to a trait /condition.
- X-dominance can be distinguished from autosomal dominant inheritance by the lack of male to male transmission.
- Affected fathers with normal mates transmit the disorder to all the daughters, but none of their sons.
- Each child of an affected female has a 50% chance of inheriting the trait, regardless of sex.
- Affected females typically have milder expression of the phenotype.
- Some rare genetic defects expressed exclusively in females appears to be X-dominant lethal in males before birth or at early infancy like Rett syndrome. Males who survive with the syndrome usually have two X chromosomes with the male determining SRY gene translocated to an X **(Fig for pedigree pattern of XD disorders).**

Name of the disease	Symptoms	Inheritance
Hemophilia	Inability of blood-clotting	XR
Duchenne muscular dystrophy	Progressive and degenerative muscle weakness.	XR
Colour blindness	Insensitivity to red/green light	XR
G6PD deficiency	Deficiency of Glucose 6-phosphate dehydrogenase, anaemia	XR
Ichthyosis	Deficiency of steroid sulfatase, scaly dry skin	XR
Lesch-Nyhan syndrome	Mental retardation, self-mutilation, early death.	XR
Vitamin D-resistant rickets	Bone deformities, particularly in lower limbs	XD
Alport syndrome	Progressive loss of hearing and progressive renal failure.	XD
Rett syndrome	Spastic and autistic child, neurobiological disorder	XD
TSPY	Testis-Specific Protein	Y
SRY	Testis determining factor	Y

10.10 Calculating frequencies for X-linked traits

The probability of any individual female having the allele in question on both X chromosomes will be q^2 and any male receiving an X chromosome with the allele must be equal to the frequency of the allele.

To illustrate for recessive X-linked trait let us consider the example of red-green color blindness, which affect 8% of the male offspring. The frequency of color-blindness allele is therefore 0.08 that means 8% of X chromosome carry it. The other 92% of the X chromosomes carry the dominant allele for normal red green colored vision.

If we define p as frequency of normal allele and q as frequency of color-blindness allele then p = 0.92 and q = 0.08.

The frequency of color-blind females (with two affected X chromosomes) = $q^2 = 0.0064$

The frequency of carrier females (with one normal and one affected X chromosomes)

$= 2pq = 2 \times 0.92 \times 0.008 = 0.147$

Therefore, 14.7% of the female carry the allele for red green color-blindness and can pass it to their offspring, although they have normal vision.