UNIT 4 SEX LINKAGE AND DOSAGE COMPENSATION

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4.1 INTRODUCTION

One of the probable deductions from your study of Mendel's laws of inheritance and their extensions and modifications in Units 1 and 2 may be that contribution to inheritance is equal from bath the parents. But sex linkage is a major exception to it. Sex linkage occurs when a gene controlling a trait is located on the'scx chromosome. The sex chromosome bears several genes in addition to those directly concerned with sex determination. The inheritance of these genes Follows a characteristic pattern which is different from that seen in the examples of monohybrid and dihybrid inheritance, that you have studied so far. The unique sex-linked pattern(s) of inheritance of any particular trait can be easily recognised and studied by pedigree analysis.

Sex linkage forms the main theme of this unit. But we begin by a brief discussion on mcndclian factors that we now know are the genes and are locatcd on the chromosomes. Then you will study examples of genes located on the sex chromnsomcs and their mode of transmission to the next generation. These would he explained with examples of X-, and Y-linked genes.

In Unit 3, you have seen that the sex chromosomes exhibit dimorphism. Due to the difference in chromosome complement there is inequality in dosage of genes present on the X chromosome in males and females. The Y chromosome bears gcnes mostly related to male differentiation. The X chromosome carries genes necessary for mediating some of the basic functions. Females with two X chr mosome would then have the X linked genes in double the dose, whereas males would have the same genes in a single dose. A dosage compensation mechanism operates to equalise the X linked gene activity in both the sexes. You would study the operational details and importance of this mechanism in two systems – man and *Drosophila*, in the last section of this unit.

Objectives

After studying this unit you would be able to:

- relate the chromosome theory of inheritance to sex linkage (Section 4.3,);
- distinguish the mode of inheritance between the X-linked genes and Y-linked gcnes (Section **4.3);**

- explain with the help of examples the transmission of recessive and dominant X-linked traits (Section 4.3, Subsection 4.3.1);
- explain with examples the transmission of Y-linked genes (Section 4.3, Subsection 4.3.2);
- discriminate between sex-limited and sex-influenced genes, and enumerate their role in the control of secondary sexual characters (Section 4.4);
- explain the importance of dosage compensation mechanism (Section 4.5);
- differentiate between the type of dosage compensation in mammals and *Drosophila* (Section 4.5);
- describe the existence of female mosaics with respect to X-linked traits (Section 4.5).

4.2 THE CHROMOSOME THEORY OF INHERITANCE AND SEX-LINKAGE

Soon after the discovery of Mendel's work in 1900, most geneticists accepted the particulate nature of genes. Mendel had predicted that each gamete contains only one allele of each gene instead of two. This prediction was based on the fact that there is reduction in the number of chromosomes by one-half at the time of meiosis during gamete formation.

Fig. 4.1: Thomas Hunt Morgan b. 25 Sept. 1866, Kentucky, d. 4 Dec. 1945, California.

This notion, that chromosomes carry genes is the **Chromosome Theory of Inheritance.** The credit for the Chromosome Theory of Inheritance goes to Walter Sutton and Theodor Boveri. In 1902, these investigators independently recognised that the behaviour of Mendel's genes during production of gametes in peas precisely paralleled the behaviour of chromosomes at meiosis. The following parallels were drawn between the two: i) genes are in pairs, so are the chromosomes, ii) the members of gene pair segregate equally into gametes, so do the members of a pair of homologous chromosome, and iii) the different gene pairs act independently, so do the different chromosome pairs.

The proposition of the Chromosome Theory was a crucial new step in genetic thinking at that time. No longer were genes just disembodied factors, now they were a part of the observable entities in the cell nucleus. Some geneticists, particularly, Thomas Hunt Morgan (Fig. 4.1) remained skeptical of this idea. Ironically it was Morgan himself who in 1910 provided the first definitive evidence for the Chromosome Theory based on his studies on sex linkage.

Morgan worked with fruit fly *Drosophila melanogaster*. When he mated red-eyed flies R R (dominant) with white-eyed flies r r (recessive), the F_1 progeny were red-eyed. Furthermore, when Morgan mated red-eyed males of the F_1 generation with their red-eyed sisters, they produced about 1/4 white-eyed males, but no white-eyed females. In other words, the eye colour phenotype is X-linked. X-chromosome and eye colour are transmitted together because the genes governing this character are located on the X-chromosome. In a diploid individual, we know, the autosomes occur in pairs but as regards to X-chromosomes the female fly has two copies and the male has just one. However, Morgan was reluctant to draw this conclusion until he observed sex-linkage with two more characters – miniature wings and yellow body in the fruit fly. That was enough to convince him and other geneticists of the validity of the chromosome theory of inheritance.

4.3 SEX-LINKED INHERITANCE

The inheritance of genes located on the sex chromosomes follows a characteristic pattern which is different from those located on the autosomes. You are already familiar with this concept from your study of Section 2.7 of Unit 2, where we have discussed Morgan's discovery of sex linkage in *Drosophila*. You may revise that portion again before you begin your study of this section. Here, we are elaborating

on the XX-XY system as it pertains to man and most of the examples cited are also of human context.

4.3.1 X-Linked Traits in Humans

Let us first examine traits determined by genes on the X-chromosome, or the *X-linked traits.* The human *X* chromosome contains many genes that are required in both the sexes, whereas the Y chromosome contains only a few genes, principally the genes for maleness. More than two hundred traits have been found to be X-linked and only a few are known to be Y-linked. The traits controlled by genes located on the X-chromosome are also referred to as **sex-linked.** That is, the terms X-linked and sex-linked are used synonymously. It is more appropriate, however, to refer to these as X-linked traits, since they follow the pattern of transmission of the X-chromosome.

The X-linked traits have a unique mode of inheritance because females have two doses of X-linked genes, while males have only one. Males are thus hemizygous for X-linked traits.

X-Linked Dominant Genes

Dominant X-linked genes are always expressed in both the sexes just as in autosomal traits. One dose of X-linked dominant allele produces its effects in males as well as females. The hemizygous male transmits the gene to all its daughters but none to his sons. There is no father to son transmission. The heterozygous females transmit the trait to half their children, irrespective of their sex. On the other hand, females homozygous for the dominanl allele produce all affected children. For example, a form of vitamin D-resistant rickets is inherited as an X-linked dominant trait (Fig. 4.2).

X-Linked Recessive Genes

The opposite is true for recessive alleles. Males being hemizygous, always express the **recessive X-linked alleles.** Females, however, express recessive alleles only when they are homozygous. Thus, the **frequency of X-linked recessive traits is always lower in females than males.**

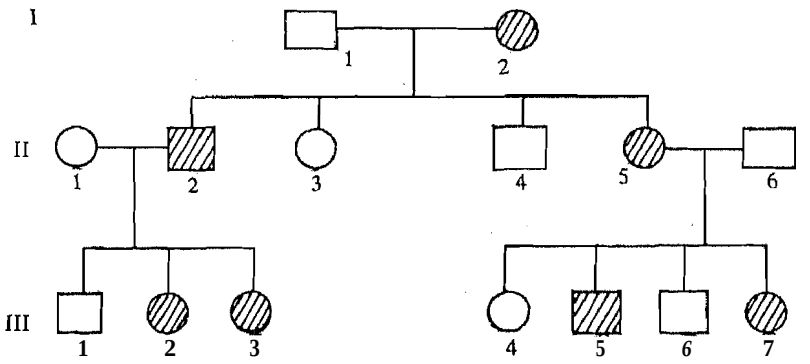

Fig. 4.2: Pcdigrec demonstrating X-linked dominant trait. The affected progeny are shaded.

Most X-linked genes are recessive alleles, and they are discovered when their deleterious effects appear in males. Males transmit their X chromosome to every daughter, and their Y chromosome to every son. *Recessive X-linked traits thus show a pattern of inheritance, in which the phenotype is usually expressed only in males of alternate generations.* A male bearer transmits the recessive allele to daughters, who does not express the allele because it occurs in the heterozygous condition. However, each of her male offspring has a 50% chance of receiving that allele and expressing the phenotype. The trait should thus appear in 1/4 of her offspring (1/2 of her offspring are expected to be male and 1/2 of her sons receive the recessive allele: $1/2 \times 1/2 = 1/4$). The heterozygous female is a carrier of the allele. The X-linked allele is often said to show a **criss cross** pattern of inheritance. In this pattern of inheritance, the allele is transmitted from male to female, female to male, and the trait is expressed only in males in alternate generations (see Fig. **4.3).** Well-known examples of X-linked recessive alleles include Red green colour blindness, Haemophilia, Glucose-6-phosphate dehydrogenase deficiency (G-6PD), Congenital hyperuricemia, Duchenne muscular dystrophy, and Ichthyosis.

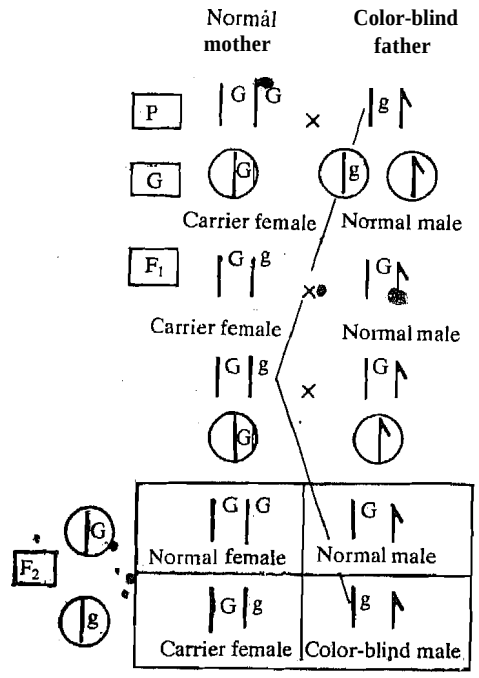

Fig. 4.3: Criss cross inheritance, i.e., the inheritance of a character trom father to daughter to grandson. It is characteristic of a sex-linked gene. Genes are shown on the chromosomes illustrating a cross between a woman with normal vision and a green-rolour defective man. The symbol *g* represents the sex-linked recessive gene for green colour defective vision, and *G* the normnl condition.

SAQ 1

A husband and wife arc normal although both their fathers have a trait wiich is X-linked recessive. What is the probability that their first child will be:

a) **A** normal son?
b) a normal daughter?
c) a son with the trait?
d) a daughter with the trait?

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Red Green **Colour** Blindness: Many persons cannot perceive certain colours. The most common such defect is an inability to distinguish red from green. This condition is also called partial **colour blindness.** Colour perception is controlled by the cone-shaped cells in the retina of the eye. Three types of cone cells, each containing a specific light absorbing pigment (whose nature is protein), that perceives a specific portion of the visible spectrum (see Fig. 4.4) have been identified. These three types of cone cells are referred to as red-absorbing, green-absorbing and blue-absorbing cone cells.

By 1986, the genes that encode the above three light-absorbing pigments of the retina were isolated and their nucleotide sequence was determined. The sequences have been used to find out the amino acid sequences of the three light absorbing proteins. These light-absorbing proteins were found to have very similar structures. See Fig. 4.5, the red and green-receptor proteins differ at only a few of the amino

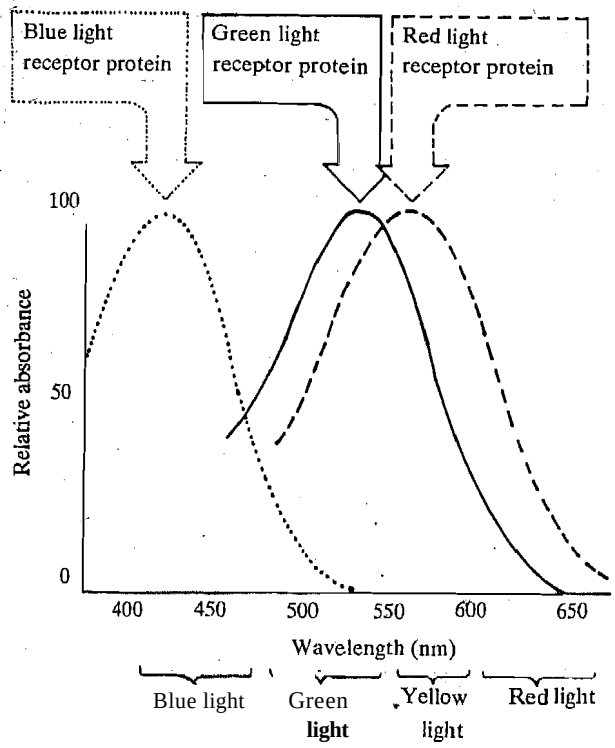

Fig. 4.4: Absorption spectra of the blue, green and red proteins present in the cone cells of the retina of the human eye. The ability of humans with normal colour vision to distinguish colours throughout the visible spectrum depends on the presence of all three proteins. Defective colour vision results from the absence of, or a defect in, one or more of these proteins. [After *Nathans, J.* 1989. *The Genes for:colour vision, Sa. Amer. 260(2): 42-49].*

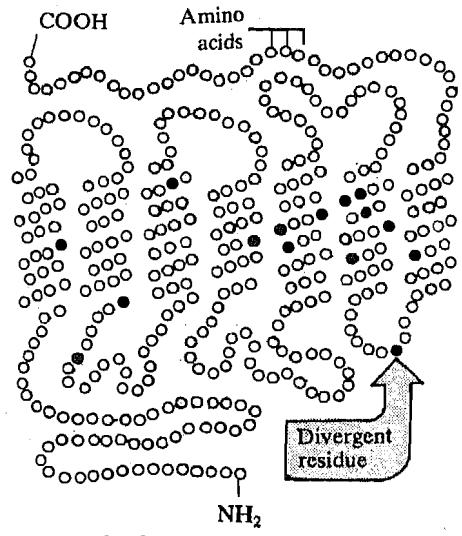

Fig. 4.5: The diagrammatic representation of the structure of red and green receptor proteins of humans. Each circle represents one subunit (amino acid) of each of the protein. Note the difference in the two proteins. [After *Nathans, J. 1989. The Genes for Colour Vision, Sci. Amer. 260(2): 42-49].*

acid subunits. The genes that encode the green-, and red-receptor proteins are located on the X-chromosomes, thus the sex-linked patterns of inheritance are observed for defects in green and red colour vision. And the gene encoding the blue receptor protein was found to be located on chromosome-7, that is, an autosome. Let us now examine some crosses (see Fig. 4.6) and assess the pattern of inheritance of this defect. For the sake of simplicity we are only considering here one gene, that is, gene causing defects in the green receptor protein, as a single sex-linked recessive allele. Since the Y chromosomes carried no colour vision locus, the single allele is expressed causing colour blindness. Stop here for a minute and carefully study the five crosses in the figure. The symbol G denotes normal receptor pigment, and g is for the defective receptor pigment causing colour blindness.

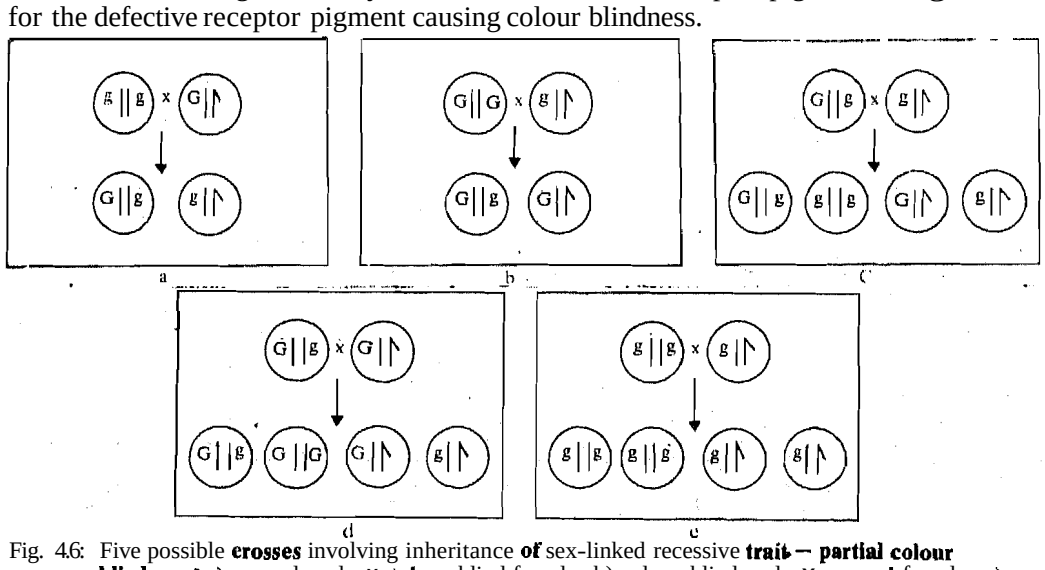

Fig. 4.6: Five possible crosses involving inheritance of sex-linked recessive trait – partial colour blindness: a) normal male x colour blind female; b) colour blind male x normal female; c) colour blind male x normal female who is a carrier; d) normal male x normal female who is a carrier; e) colour blind female x colour blind male.

In the above crosses have you noticed that sex-linked inheritance does not conform to the Mendel's laws of inheritance? Fig. 4.6 shows the results of reciprocal matings of affected and unaffected parents. The normal male and colour'blind (recessive, homozygous) female produce normal but heterozygous daughters, but all sons have the disease (cross a). The reciprocal cross (b) demonstrates criss cross inheritance. A colour blind male (hemizygous) with a normal (homozygous) female produces no affected offspring, but the daughters are carriers (cross b). A colour blind male and a carrier female result in 50% colour blinds (see cross c). Another possibility, a normal male mated with a carrier female, produces all normal female offspring but 50% affected male offspring (see cross d). The mating of two colour blind individuals result in all colour blind offspring (see cross e) if they have the same colour blindness.

Haemophilia: Haemophilia is a disease in which one of the factors required for the normal clotting of blood (see Fig. 4.7) is deficient. As a result, the blood fails to clot or clots very slowly. Thus even minor injuries can cause profuse internal and external bleeding which can lead to death.

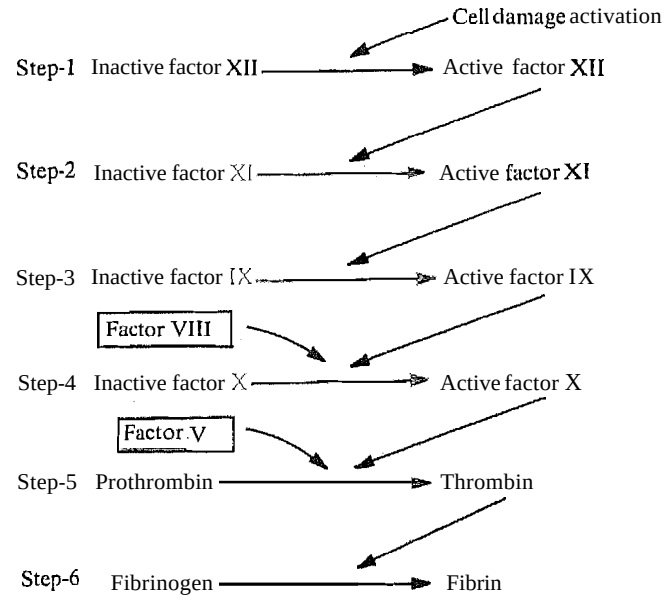

Fig. 4,7: Blood clotting is the end result of a series of reactions requiring various enzymes and cofactors, leading to the formation of insoluble fibrin. Many of the steps in the chain entail the conversion of a gene product to its active enzymatic form by the enzymatic action of the active product of a previous step. Cofactors (e.g., factor VIII and V) are required to work along with some of the active enzymes. Factor VIII, absent/defective in haemophilia A, is a cofactor required along with factor IX to activate factor X. If factor VII is absent as a result of a sex-linked recessive condition, the sequence is interrupted and the end result is defective clotting. In haemophilia B, factor IX is deficient.

Three forms of haemophilia controlled by three different gene loci are known. One of them is rare and is controlled by an autosomal recessive gene, while two forms, that is, haemophilia A and B result from recessive alleles at two X-linked loci. Haemophilia B also known as *Christmas disease,* comprises about 20% of all haemophilia and is caused by the deficiency of factor IX (see Fig. 4.7, step **3).**

Haemophilia **A,** classical haemophilia is caused by an abnormality or deficiency of a protein cofactor known as factor VIII is located on X-chromosome. Factor VIII is needed for the activity of one of the enzymes – factor IX, in the series of events leading to the activation of thrombin. Absence of functional factor VIII interrupts the steps leading to the activation of thrombin, and consequently fibrin cannot form. Until recently, haemophilia A was untreatable and only about 25% of the affected males reached age of twenty five. Treatment with factor VIII now results in a longer life span.

The frequency of haemophiliacs is about one in ten thousand males, but is much lower in females, about one in one hundred million or less. A female hacmophiliac can result from the mating of a heterozygous female with an affected male. Such a mating, is highly unlikely because very few male haemophiliacs survive long enough to reproduce. Haemophiliac females are also belived to die at the onset of menstruation.

Haemophilia is one of the earliest known diseases, According to Talmud, the Hebrew book of law, when excessive bleeding occurred during circumcision of two male infants of a mother, future male offspring were exempt. When sons of three sisters exhibited bleeding, sons of other sisters were also exempt. However, sons of brothers were not exempt, implying an understanding of criss cross pattern of inheritance.

Haemophilia A has been called the "Royal disease" because it affected males in the royal families of Europe. Queen Victoria, a carrier of the haemophilia allele had nine children (Fig. 4.8). Her eighth child, Leopold was a haemophiliac who died at the age of thirty one. Her other three soils were unaffected as they did not receive the allele. One daughter had no children, her status as a carrier cannot be assessed. Two daughters had children, none of whom were haemophiliac, indicating that mothers probably were not carriers. Two other daughters were carriers giving birth to haemophiliac sons.

The possible historical influence of haemophilia is tentalising. Victoria's third child was princess Alice, whose daughter Alexandra married Czar Nicholas II of Russia. The Czarina, Alexandra, had four'daughters before giving birth to the long awaited son Alexis – the heir to the Russian throne. Unfortunately, Alexis had the haemophilia allele, a legacy from his great grand mother – Queen Victoria. Distressed over their son's condition, the Czar and Czarina turned to the monk Kasputin. While affairs of the state deteriorated, culminating in Russian revolution, the Czar was preoccupied with the health of his son.

Among Victoria's descendants, eight of twenty five males in four generations were haemophiliacs. Queen Victoria almost certainly received the gene for haemophilia A, as a result of mutation on the X chromosome which she received from her father Edward, Duke of Kent. He was fifty-two years old at the time of Victoria's birth and such mutations may occur more frequently in the germ cells of older males.

In the recent years, a serious threat to victims of haemophilia has arisen due to their continuing dcpendencc upon blood transfusions. Such transfusions are one means of transferring Acquired Immune Deficiency Syndrome (AIDS) and some haemophiliacs have infact acquired AIDS in this way. Extensive surveillance of donor blood supplies is required to protect haemophiliacs and all others requiring transfusions.

Glucose 6-Phosphate **Dehydrogenase** (G-6PD) Deficiency: Another disease due to defective X-linked rccessivc allele is G-6PD. This is an important enzyme, for carbohydrate metabolism and maintaining stability of red blood cells.

Deficiency of enzyme G-6PD is a rare condition characterised by severe haemolytic anaemia (due to destruction of red blood cells) when exposed to environmental triggers such as fava beans, naphthalene and certain sulpha drugs.

Congential Hyperuricemia – Lesch-Nyhan Syndrome: This disease is characterised by the excess production of uric acid. A mother contributes the X-chromosome with defective genc to a male zygote. Half of the male children of carriermothers may be expected to inherit the disease. They are deficient for the enzyme

hypoxanthine-guanine phosphoribosyl trsnsferase (**HGPRT**). This enzyme is involved in nucleotide synthesis. Infants who receive the genc appear normal at birth. The initial symptom of the disease is the production of excessive uric acid in the urine as a result it appears as orange sand-coloured. By 10 months of age, the patients become abnormally irritable and lose motor control. Weak and flabby muscles prevent the child from sitting, walking and speaking normally. As the disease advances, there is deterioration of nervous system. Self-mutilation occurs, manifested by lip-biting, finger-chewing, teeth-grinding, and marked swinging of the arms. Eventually death occurs within a few ycars due to severe renal and neurological damage. Some of the patients live to their twenties.

Duchenne Muscular Dystrophy (DMD): It is another example of an X-linked recessive allele, that primarily affects young males. Half of the male progeny of a carrier female are expected to be affected. In the affected males deterioration begins between the ages of three and five years, but sometimes the affected individuals reach their teens. But they are confined to wheel chairs; and they die in their early twenties due to atrophy of their respiratory muscles. Only few affected malcs reproduce, so the condition is transmitted rnainly by female carriers. This disease occurs in about one in every four hundred newborn males; and is several times more frequent then haemophilia. In 1986, the defective gene that causes DMD was isolated and studied. It was found that the absence or a protein - *dystrophin* caused DMD.

Ichthyosis: So far you have seen the examples where the recessive X-linked are expressed in males. There are, however, instances where these are also expressed in females in certain situations. **Consanguineous matings** (see adjacent Margin Remark) can greatly increase the frequency of expression of X-linked traits in females. In consanguineous pedigrees containing X-linked recessive alleles, females have a high probability of carrying the X-linked allele, as they can receive the allele from either parent. In turn, matings of carrier females and affected males (Fig. 4.9) produce daughters and sons with an equal likelihood (i.e., 50%) of being affected.

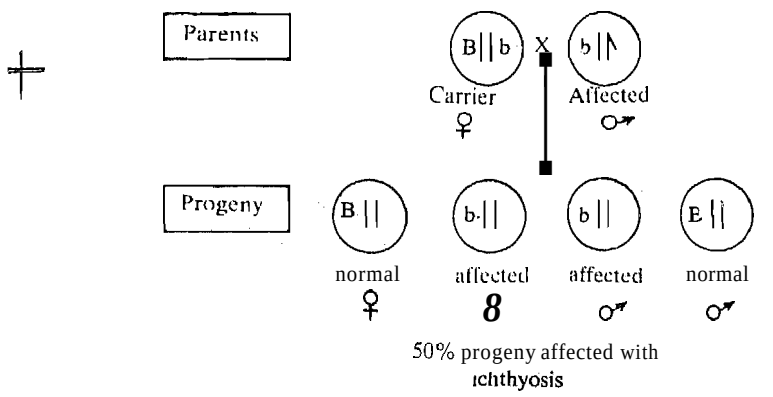

Fig. 4.9: **Cross between ichthyosis** currier **female and affected male showing 50% affected progeny.**

Consanguineous means "of the same blood". The term means sharing genes derived from a common ancestor, related by descent.

Ichthyosis is a disorder characterised by extreme dryness, roughness and scaliness of the skin. The prefix 'ichthy' means fish-like. Children produced in situation as shown in Fig. 4.9 show ichthyosis at birth. Similarly, Fig. 4.10 shows a pedigrees of a family in which consanguineous mating resulted in expression of this X-linked trait in females. The allele for ichthyosis first appeared in male I-1. His first four daughters all transmitted the allele, without expressing the condition themselves. Male III-11 mated with his first cousin, once removed IV-3, who must have been a carrier, having received the ichthyosis allele through two generations of females. One of their three sons and two of their three daughters exhibited ichthyosis, a highly unlikely result without consanguineous mating.

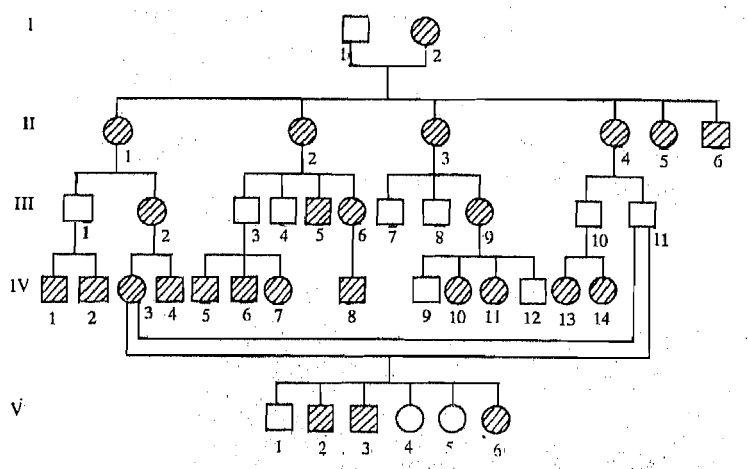

Fig. 4.10: **A pedigree showing the occurrence of a X-linked recessive trait, ichthyosis in females as a result of consanguineous mating.**

Before we go on to the next subsection, how about trying a couple of SAQs?

SAQ 2

A couple have a colour blind daughter and son with normal vision. What are the genotypes of the parent in this cross?

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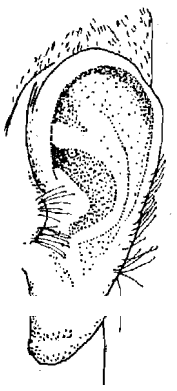

Fig. 4.11: Hairy ear in humans, a trait which is determined by a Y-linked gene.

SAQ 3

Draw a three generation pedigree of a family starting from a couple, where male is a haemophiliac and the female is normal. They have 3 sons and a carrier daughter. The daughter marries a normal male and has 3 daughters and 2 sons. What is the probability of her children being carriers and haemophiliacs?

4.3.2 Y-Linked Traits in Humans

Any gene that occurs exclusively on the Y chromosome is said to be **holandric** and it is not expressed in females. Such a Y-linked gene normally occurs in males and is transmitted only from father to son – **holandric inheritance.** Only a few Y-linked genes have been identified uptil now. One is the histocompatibility gene, known as the H-Y gene which is present on the short arm of the Y chromosome. Another important Y-linked gene is the TDF gene that codes for testis determining factor. This locus plays an important role in primary sex determination. The functional significance of TDF gene would be explained in Unit 5.

Another phenotype known to be associated with the Y chromosome is the condition **hypertrichosis.** The gene concerned with this condition leads to the development of hairy pinna (Fig. 4.11). This phenotype has been observed in the inhabitants of Australia, Ceylon, Israel, and India.

SAQ 4

A man has hypcrtrichosis of the ears, a condition due to a gene on the Y-chromosome. Show the types of male and female children he has.

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SAQ 5

Is a Y-chromosome linked gene supposed to be dominant or recessive in order to be recognised? How is a Y-linked gene transmitted to grand children?

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4.4 SEX-LIMITED AND SEX-INFLUENCED TRAITS

Not all of the characters that differ in the two sexes are X-linked. There are certain traits that arc determined by autosomal genes, but their expression is altered or influenced by the sex of the individual. Many a times these traits are confused with the sex-linked traits. Actually, they are entirely different in their mode of inheritance since their genetic determinants arc not located on the sex chromosomes. There are two kinds of such traits: sex-limited, and sex-influenced traits.

4.4.1 Sex-Limited Traits

Sex-Limited Traits are traits expressed only in one sex, although the genes controlling them arc prcscnt as well as transmitted to both the sexes. Therefore, males and females with the same genotype, with rcspcct to a particular locus may have different phenotypes.

Sex-Limited Traits are determined by autosomal genes, whose phenotypic expression is determined by the presence or absence of one of the sex hormones. Since sex hormones are the limiting factors, the phenotypic expression of these genes is limited to one sex or the other. The most obvious examples are the secondary sex characteristics. Beard development in human beings is one such sex-limited character as men have beards, and woman normally do not. Yet studies indicate no significant differences between the sexes in number of hairs per unit area of skin surface except in their development. This appears to clepend on sex hormone production. Any disturbance in these hormones in women may result in the development of beard. Similarly, the full development of breasts in females, and presence of prostate glands in males are the examples of sex-limited traits seen in human beings. Traits like egg laying in chickens, oviposition behaviour in insects are some other such examples. Milk production in mammals is limited to females, but certain bulls are in great demand among dairy breeders and artificial insemination associations because their mothers and daughters have increased milk production records.

Another classic example of a sex-limited trait is "cock feathering" in different birds. Wc consider here the example of domestic fowl, the males and females exhibit pronounced difference in their plumage. In the *leghorn* breed the males have long, pointed, curved, fringed fcathcrs on tail and neck, but feathers on females are shorter, rounded, straighter, and without fringe (see Fig. 4.12). Thus males are cock-feathered and females arc hen-feathercd. In the breeds *Sebright bantam,* birds of both sexes arc hen-feathered. However, in *Hamburg* and *Wyandotte,* both hen-, and cock-feathered males are seen, but all the females are hen-feathered. The feathering type clepcnds on a single pair of alleles H and h in the following manner (Table 4.1).

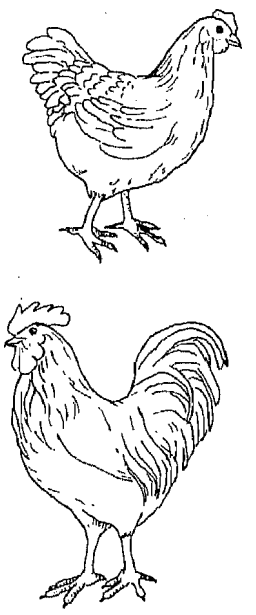

Fig. 4.12 : Hen-feathering (top), and cock-feathering (bottom) in domestic fowl.

Table 4.1: The Feathering Type in Domestic Fowl.

Genotype	Male	Female
HH	hen-feathered	**hen-feathered**
Hh	**hen-feathered**	**hen-feathered**
hh	**hen-feathered**	**cock-feathered**

Thus *Sebright bantams* are all HH. *Hamburgs* and *Wyandottes* may be *H–*, or hh, and *Leghorns* are all *hh.* Cock-feathering where it occurs is limited to the male sex.

4.4.2 Sex-Influenced Traits

Sex-Influenced or Sex-Controlled **Traits** appear in both sexes but occur in one sex more than the other.

The genes for Sex-Influencerl Traits show differing patterns of expression in each sex-usually the trait behaves as dominant in one sex and a recessive in the other. Genes for sex-**influenced traits occur** only on **autosomes.**

Heredity and Phenotype

Pattern baldness refers to a definite genetic pattern. In this condition hair usually thins on top ultimately leaving a fringe of hair low on the head (Fig. 4.13). Baldness may also arise due to various causes such as disease, radiation, thyroid defect.

The best documented example of sex-influenced inheritance is **pattern baldness** (Figs. 4.13 and 4.14). Individuals expressing pattern baldness begin to lose their hair on the front and the top of the head, relatively early in life, often in their twenties. Affected individuals are not totally bald: a distinct rim of hair surrounds their head in patterns varying from person to person. It has been proposed that a single pair of alleles is involved. The allele B_1 which is responsible for pattern baldness is dominant in males, and the heterozygous males therefore, express pattern baldness. In females, however, the gene is recessive. The allele for normal hair growth can be designated as B_2. Individuals with the genotype $B_1 B_1$ show pattern baldness, regardless of sex. In such situations, in females there is marked thinning, rather than total loss of hair on the top of the head. Persons with B_1B_2 genotype are bald if they are male but not bald if they are female. *The presence of male hormones, are strongly implicated in the expression of pattern baldness.*

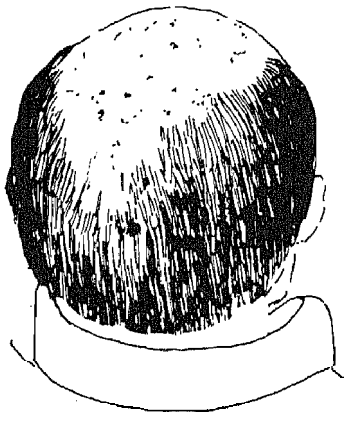

Fig. 4.13: Pattern-baldness in man.

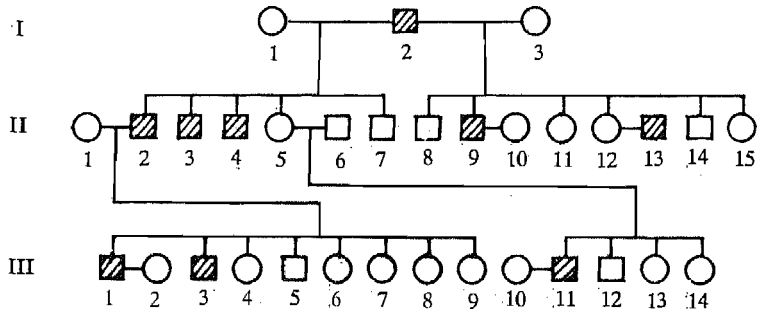

Fig. 4.14: Pedigree showing the incidence of pattern baldness in a family. The men represented by the dark squares became bald before they reached the age of 35. Those represented by light squares are over 35 and have thick hair. No woman in this family pedigree expressed the trait (After *Gardner el al. 1991, Principle of Genetics, John Wiley & Sons, Inc.*)

Some human traits, such as certain types of white forelock, abscncc of upper lateral incisor teeth, a particular type of enlargement of the terminal joints of the fingers, and cleft-lip, exhibit a pattern of inheritance characteristic of sex-influenced genes.

A few well-known examples of sex-influenced genes in animals are: spotting in cattle (mahogany and white dominant in males, red and white dominant in females), horned versus hornless condition in sheep (Fig. 4.15) where the autosomal gene involved is dominant in males and recessive in females.

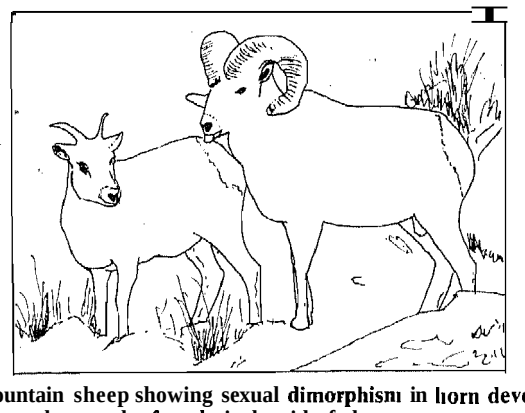

Fig. 4.15: Rocky mountain sheep showing sexual dimorphism in horn development. The male has large horns, whereas the female is devoid of them.

SAQ 6

Compare the inheritance pattern of the sex-limited traits with those of the sex-linked traits.

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4.5 DOSAGE COMPENSATION

Recall that in the XX-XY chromosome system, males have only one X chromosome (hemizygous) while the females have two. Thus the males have half the number of X-linked genes as females. In other words, the males have only one dose of X chromosomes and the females have double dose of X-chromosomes. We know that the amount of gene product in cells is related to the number of gene copies present, it would be expected that females would have double the amount of X-linked gene products as compared to males. Now the question arises, is there any compensation for this dosage difference between sexes? The answer is 'Yes', there is a mechanism which regulates the levels of gene products in such a way that both hemizygous and heterozygous/homozygous individuals that is, males and females, have the same amount of gene product. This mechanism is known as Dosage Compensation.

4.5.1 In Man

In human and other mammals, the necessary dosage compensation is accompanied by inactivation or "turning **off"** of one of the X chromosomes in females so that both males and females have only one functional X chromosome per cell. The inactive X chromosome, in females becomes tightly coiled into **'heterochromatin'**, a condensed form of chromatin visible as a dark spot – X-chromatin or Barr body (after its discoverer M.L. Barr) in the nucleus of female cell (Fig. 4.16.). Thus Barr body is the inactivated X chromosome. One X chromosome is necessary for normal development in both sexes, but if an individual (or either sex) has more than one X-chromosomes, all but one are inactivated and are visible in stained somatic cells as Barr bodies. Thus somatic cell nuclei of normal males have no Barr body, and those of normal females have one (also see Box 4.1).

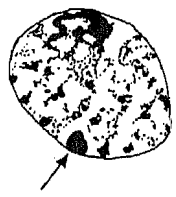

Fig. 4.16: Barr Body in the nucleus of a cell of a normal female.

Box 4.1: Detection **of Barr** Body
A simple-way to demonstrate the **Barr** Body in humans is by scraping epithelial cells from the buccal mucosa of females, and staining them with a specific dye. The nuclei in **many cells** would show a small, diamond-shaped Structure about 1 μm in diameter, more deeply stained than the surrounding chromatin and **usually** located at the periphery of the nucleus. This body stains positively in the **Feulgen** reaction for DNA.

The hypothesis that all but one *X chromosome(s) are* ***inactivated*** in each cell was proposed by the geneticist Mary F. Lyon (Fig. 4.17) in 1961 and is known as Lyon hypothesis. Crucial evidence for this hypothesis was provided by sexually aneuploid individuals. **Aneuploidy** (meaning not the true number) refers to the possession of an abnormal number of chromosomes. Aneuploid individuals have the normal diploid number, plus or minus one or more chromosomes. Females lacking one X chromosome exhibit Turner's syndrome, designated 45, XO (45 chromosomes, with one X missing). Males with an extra X-chromosome have **Klinefelter's** syndrome designated 47 XXY. Cells from 45, XO females and 46 XY males have no Barr bodies (Fig. 4.18a); while those from 47, XXX females and 48 XXXY males have two (Fig. 4.8b); 46, XX females and 47, XXY males have one Barr body (Fig. 4.18c); and '48, XXXX females and 49, XXXXY males have three Barr bodies (Fig. 4.18d). Examination of the number of Barr bodies can be done easily to screen for sex-chromosomes abnormalities. You have already seen in Box 4.1 how to make a

Fig. 4.17.: Mary F. Lyon, (1925)

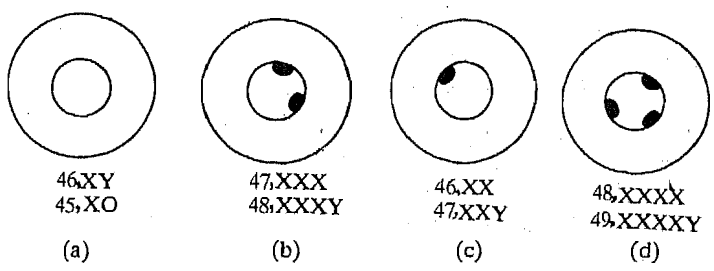

Fig. 4.18: Diagrammatic representation of varying number of Barr bodies in different genetic make ups.

preparation of the epithelial cclls from the buccal cavity for examination. The mandatory "sex tests" that have been required for Olympic athletes includes a count of Barr bodies. Males disguised as females can be identified as they have no Barr bodies.

The inactivation of X chromosomes during development occurs at random. Early in development, the maternally derived X is inactivated or lyonised in some, while the paternally-derived X is inactivated in others. Thereafter, descendants of a particular cell have the same X inactivated (Fig. 4.19). If a female is heterozygous for an X-linked gcnc, she is **mosaic** For that trait. One of her X-chromosomes is active in roughly half of her cells while the second X is active in other ccls. That is to say that some cells express X-linked genes inherited from the father while others express those passed on by the mother.

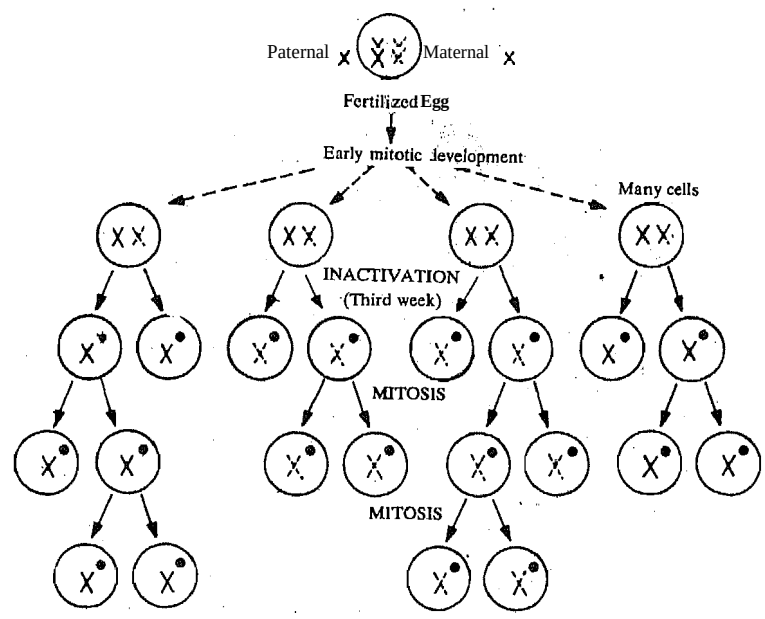

Fig. 4.19: Diagrammatic representation of the random inactivation of one of the two chromosomes in female cells, all progeny cells inactivate the same chromosome. All descendants of these cells have the same chromosome inactivated, so females arc mosaics for their maternally-derived and paternally-clerived X chromosomes.

Fig. 4.20: A calico cat with patches of colour resulting from random inactivation of X chromosomes bearing colour determining genes in cells giving rise to hair.

Calico cats (Fig. 4.20) exhibit mosaicism, due to dosage compensation. Several loci control coat colour in cats, but only one X-linked locus is involved in producing calico individuals. Two alleles occur at that locus, R and *R′*. In males (hcmizygous), R produces rust coat colour and R' black. In females R inactivation produces cloncs of R-bearing rust fur intermixed with R'-bearing black fur – the calico cat. Thus almost all calico cats are females. Male calico cats, only result because of sex-chromosome aneuplioidy. XXY males also undergo X inactivation, so an occasional calico male is seen.

When a female is hcterozygous for a deleterious X-linked allele, the effects of the cell lines bearing the normal allele may compcnsatc for the harmful cffccts of the cell lines bearing the deleterious allele. In females heterozygous for partial colour blindness, for examples, some cell clones in the retina are in fact colour blind, hut the presence of other normal clones results in normal colour vision.

X inactivation in humans can sometimes be seen in females heterozygous for certain X-linked traits. Let us elaborate this point. *Ectodermal dysplasia* is a condition known to be X-linked and it involves the lack of some teeth and sweat glands in the affected individuals. Heterozygous females show a mosaic of areas of the jaw with and without teeth and patches of skin with and without sweat glands. In Fig. 4.21, the females in generation III arc identical twins; they have developed from a single fertilised egg and are therefore genetically identical. However, due to random inactivation of different X chromosomes during development, they show considcrablc difference in the location of patches of skin lacking sweat glands. X-chromosome inactivation is one example of a development process that can produce phenotypic differences in genotypically identical individuals. Thus, even clones may differ significantly.

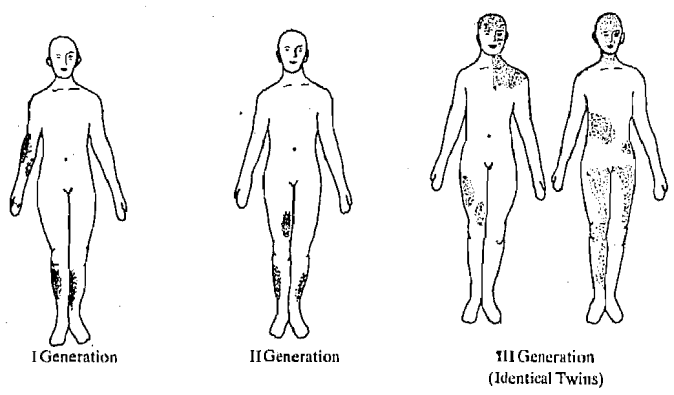

Fig. 3.21 : Three generations of females, all showing mosaic phenotypes. All the females are heterozygous for the X-linked gene for *ectodermal dysplasia.* The dark regions in the figure indicate areas in which the sweat glands are missing. Note that the affected areas differ in each woman because tlie controlling gene is inactivated randomly even in the identical twins in generation III.

Another example that shows the genetic consequences of X-inactivation in females heterozygous for an X-linked gene is the enzyme G-6PD. Cell cultures from an individual heterozygous for the G-6PD gene, has alleles with two forms of the enzyme: G-6PD type A and G-6PD type B. In spite of the cells carrying both the alleles, half the cells express G-6PD type A enzyme, while the remaining express G-6PD type B enzyme. If one cell from this culture was made to grow in isolation then all cells arising from it express the same enzyme type as its parent cell. It confirms the hypothesis that X-inactivation is clonally transmitted, i.e., the same inactivated X-chromosome is passed to daughter cells throughout repeated cell divisions.

The phenomenon of random X-inactivation enables the detection of females heterozygous for a particular trait or enzyme. Some of the cells of this female will have gene expression like deficient male cells and some like normal female cells. Detection of carriers in this way may be of great help in genetic counselling especially in case of X-linked disorders. You would study some more examples of such disorders in Unit 10 of Block 2.

The inactivation of one of the two X **chromosomes** in females **must** be **reversible,** since females transmit both of their X chromosomes to their progeny in a functional state. This is especially clear in the case of hemizygous male progeny which receives either of the X chromosomes of the mother with equal probability, because the single X chromosome that each son receives must be fully active given that the X chromosomes contains many genes that are vital to the growth and development, indeed to the survival. The **reactivation-"turning** on" of the inactive heterochromatic X chromosomes of mammalian femalcs occurs in germ cell lineages prior to oogenesis. Both X chromosomes of a female are active in the oogonial cells. The maintenance of the germ cells and ovarian structures requires the presence of two X-chromosomes. At this point you may wonder, whether normal reactivation ever fails tb occur. There are considerable evidences that indicate abnormal reactivation of the heterochromatic X chromosomes. The most common form of inherited mental retardation in humans is its example.

4.5.2 In *Drosophila*

Dosage compensation occurs in fruit flies, but its mechanism is different from those of the mammals. No barr bodies are found in fruit flies. You have already learnt that in fruit flies, the X chromosome to autosome ratio is responsible for sex determination. Normal females have two X chromosomes and normal males have one X chromosome. *Dosage compensation in this case is achieved by increased transcriptional activity of genes on the single X chromosome in male cells relative to that of each of the X chromosome in female cells.* The *male has hyperactive X-chromosome,* approaching the level of activity of both of the females

This hyperactivity of X-chromosome can be cytologically seen as "puffed" bands in the salivary gland chromosomes (Fig. 4.22). *This is in variance to the inactive X-chromosome in mammals which appears condensed (sex chromation body).*

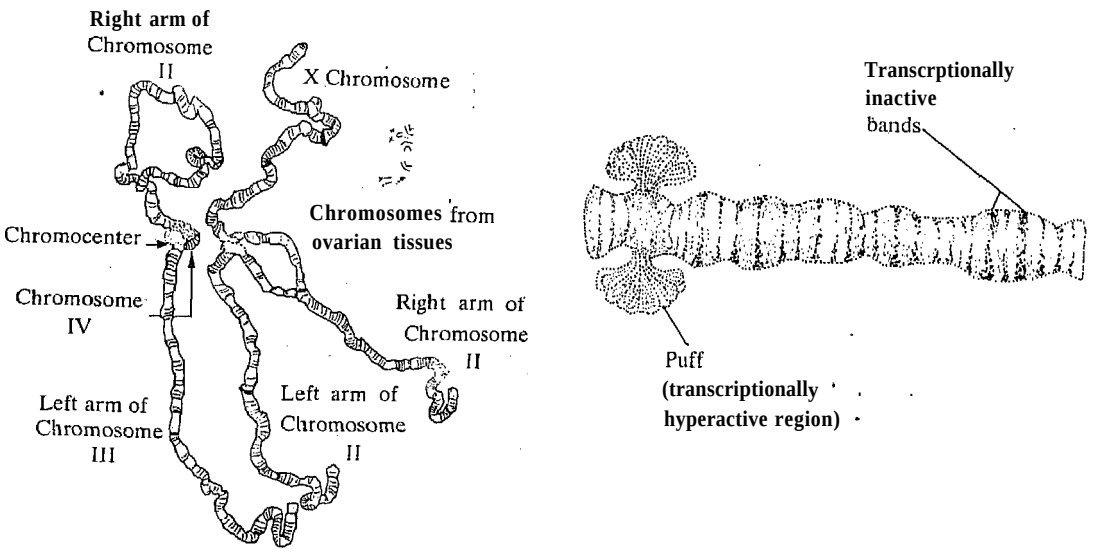

Fig. 4.22: a) The salivary gland chromosomes of *Drosophila melanogaster*. b) A portion of the puffed band enlarged.

SAQ 7

Indicate the expected number of Barr bodies in interphase cells of the following individuals: Klinefelter's Syndrome; Turner's syndrome; and Karyotypes 47 XYY, 47 XXX, and 48 XXXX.

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SAQ 8

Cat breeders are aware that kittens with the calico coat pattern are invariably females. Why?

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4.6 SUMMARY

In this unit you have learnt that:

- The chromosomes are the carriers of genes and the transmission of chromosomes from one' generation to the next closely parallels that of the genes.
- In species with an XX-XY mechanism, genes on the sex chromosomes may be X-linked or Y-linked.
- The mode of transmission of sex-linked traits is different from that of the autosomal ones.
- The dominant X-linked traits are always expressed in both the sexes.
- Recessive X-linked traits show a criss-cross pattern of inheritance. Female heterozygotes are carriers who pass the trait to 50% of their male offspring. Recessive X-linked traits are expressed far less commonly in females than in males.
- Only a few Y-linked genes have been identified and amongst them TDF (testis determining factor) plays a role in male sex determination.
- Sex-limited and sex-influenced traits are the result of genes on the autosomes. The expression of these genes is sexually dimorphic.
- Dosage compensation regulates the level of gene products in such a way that both males and females have the same amount of gene products.

- In female mammals including man, dosage compensation occurs by the inactivation of all the X-chromosomes except one (forming Barr body or bodies) whereas in fruit flies it occurs by the hyperactivation of the single X-chromosome in males.

4.7 TERMINAL QUESTIONS

1) List at least **four** criteria for identifying X-linked recessive traits from pedigree studies.

2) Choose the correct answer.

i) Which one of the following statements does not apply to human sex chromosomes?
   a) carry allelic pairs
   b) determine individual sex
   c) are identical in women
   d) are identical in man
   e) both a and d

ii) Barr bodies result from:
   a) inactivation of one X chromosome by the Y chromosome
   b) a third X chromosome
   c) inactivation of one X chromosome for dosage compensation
   d) both b and c

iii) **A** man and a woman are both affected by vitamin D-resistant rickets which is a dominant sex-linked allele. All of the female offspring of these people are affected with rickets, but some of the males are not. What are the possible genotypes of the parents?
   a) both are homozygous for the trait
   b) the woman is heterozygous for the trait
   c) the woman is hornozygous and the man is heterozygous
   d) this is not possible.

iv) The fly *Drosophila melanogaster* has a gene that codes for white eyes as recessive and X-linked. Red eyes result from the wild'type allele at the same locus. A cross between **a** heterozygous red-eyed female and a white-eyed male would produce:
   a) all red-eycd progeny
   b) all white-eyed males and all red-eyed females
   c) one red-eyed male and one white-eyed male
   d) one red-eyed female and one white-eyed female
   e) both c and d

v) The gene for pattern baldness is dominant in men, but exhibits recessiveness in women. The difference in expression results form:
   a) the gene for baldness being X-linked
   b) the gene for baldness being Y-linked
   c) the expression of the gene depending upon the hormonal balance of the individual
   d) both a and c
   e) none of the above

3) Fill in the blanks:

i) Men have _____ pairs of autosomes and one _____ pair of sex chromosomes.

ii) Women have _____ pairs of autosomes and one _____ pair of sex chromosomes.

iii) The fertilisation of an egg by a Y sperm results in a _____ offspring,

iv) Genes which are Y-linked are called _____.

v) Sex-limited genes are those whose phenotypic expression is determined by the presence or absence of sex _____.

vi) Beard development in humans is generally limited to one sex (male), yet studies indicate that there is no real difference in the number of hairs per unit area of skin between men and women. This indicates that beard development is a _____ trait.

4) Match the terms in column A with their appropriate descriptions in column B:

A	B
i) Dosage compensation	a) X-chromatin
ii) Turner's syndrome	b) inactivation of one X chromosome
iii) Klinefelter's syndrome	c) inactivation of one X chromosome so as to reduce to half the allele
iv) Barr body	d) inactivation of all but one X chromosome
v) Lyon hypothesis	e) phenotypically Female (XO)
	f) phenotypically male (XXY)

5) In sheep, the gene h^+ for the horned condition is dominant in males and recessive in females. If a hornless ram were mated to a horned ewe, what is the chance that:
   a) an F_2 male sheep will be horned or
   b) an F_2 female sheep will be horned?

6) In chicken, the gene h, which distinguishes hen-feathering from cock-feathering, is sex-limited. Males may be hen-feathered or cock-feathered, but females arc always hen-feathered. If a cock-feathered male (hh) were mated to a homozygous (h^+h^+) hen-feathered female, what patterns of feathering might be expected among the (a) male F_2 and (b) female F_2 progeny'?

7) In *Drosophila,* the gene for bobbed bristles (recessive allele bb, bobbed bristles; wild-type allele bb^+, normal bristles) is located on the X chromosome and on a homologous segment of the Y chromosome. Give the genotypes and phenotypes of the offspring from the following crosses: a) $X^{bb}X^{bb} \times X^{bb}Y^{bb+}$, b) $X^{bb}X^{bb} \times X^{bb}Y^{bb}$ c) $X^{bb+}X^{bb} \times X^{bb+}Y^{bb}$, d) $X^{bb+}X^{bb} \times X^{bb}Y^{bb+}$.

8) Make **a** diagram of a cross between a normal woman (whose father was defective in green colour vision) and a green colour-defective man. Suminarise the expected results for sex and colour vision.

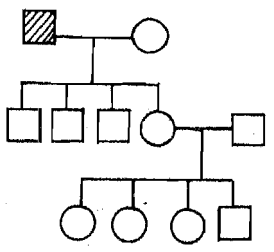
4.8 ANSWERS

Self-assessment Questions

1) Since both the husband and wife have fathers with the X-linked trait, the husband will not carry the trait as it receives its X-chromosome from his mother, but the wife carries the trait as she gets one X-chromosome from her father. a) The probability of having a normal son is fifty per cent. b) The chances of having a normal daughter is hundred per cent as a female is not affected with X-linked recessive trait unless she receives two genes for the trait. c) There is fifty per cent probability of having affected son, d) There is no chance of the daughter being affected, but there is a fifty per cent probability that they may be carrier.

2) Since the daughter is colour blind it can bc assumed that both parents carry the genes for the trait. The father's genotype is therefore, hemizygous and that of the mother is heterozygous for the trait. The son must have reccivcd the normal X-chromosome from the mother and is therefore, normal.

3)



The probability is fifty per cent for the daughters being carriers and there is fifty per cent probability of the son being a haemophiliac.

4) Only the male children have hypertrichosis ear as the gene for it is Y-linked and the Y is passed from father to son. Females don't have the trait as they never possess a Y-chromosome.

5) Irrespective of whether a Y-linked gene is recessive or dominant it can bc recognised as it is always present in hemizygous condition. The Y-linked gene is transmitied from grandfather to male grand-children through the father. The female grand-children are unaffected so are the daughters and the grand-child& born from them.

6) Sex-linked inheritance patterns **are quite** different from those of sex-limited ones. The latter may be expressed in either sex, though with differential frequency. Genes for sex-limited traits express their effects in only one sex or the other and their action is clearly related to sex hormones. They arc principally responsible for secondary sex characters.

7) Klinefelter-one; Turner-none; 47 XYY-none; 47 XXX-two; 48 XXXX-three.

8) Because the mosaic coat pattern is due to the expression of sex-linked heterozygous alleles according to the Lyon hypothesis.

Terminal Questions

1) i) The trait occurs more frequently in males than in females.
   ii) Traits are transmitted from an affected man through his carrier daughters to half his grandsons.
   iii) An X-linked allele is never transmitted directly from father to son.
   iv) All affected females have an affected fathcr and a carrier or affected mother.

2) i) e
   ii) c
   iii) b
   iv) e
   v) c

3) i) 22, XY
   ii) 22, XX
   iii) male
   iv) holandric
   v) hormones
   vi) sex-limited

4) i) b
   ii) e
   iii) f
   iv) a
   v) d

5) a) 3/4
   b) 1/4

6) a) 3 hen-feathered : 1 cock-feathered
   b) All hen-feathered

7) a) 1/2 $X^{bb}X^{bb}$ bobbed females, 1/2 $X^{bb}Y^{bb+}$ wild males;
   b) 1/2 $X^{bb}X^{bb+}$ wild females, 1/2 $X^{bb}Y^{bb}$ bobbed males;
   c) 1/2 $X^{bb+}X^{bb+}$ and $X^{bb}X^{bb+}$ wild females, 1/4 $X^{bb+}Y^{bb}$ wild males, 1/4 $X^{bb}Y^{bb}$ bobbed males;
   d) 1/4 $X^{bb+}X^{bb}$ wild females, 1/4 $X^{bb}X^{bb}$ bobbed females, 1/2 $X^{bb+}Y^{bb+}$ and $X^{bb}Y^{bb+}$ wild males