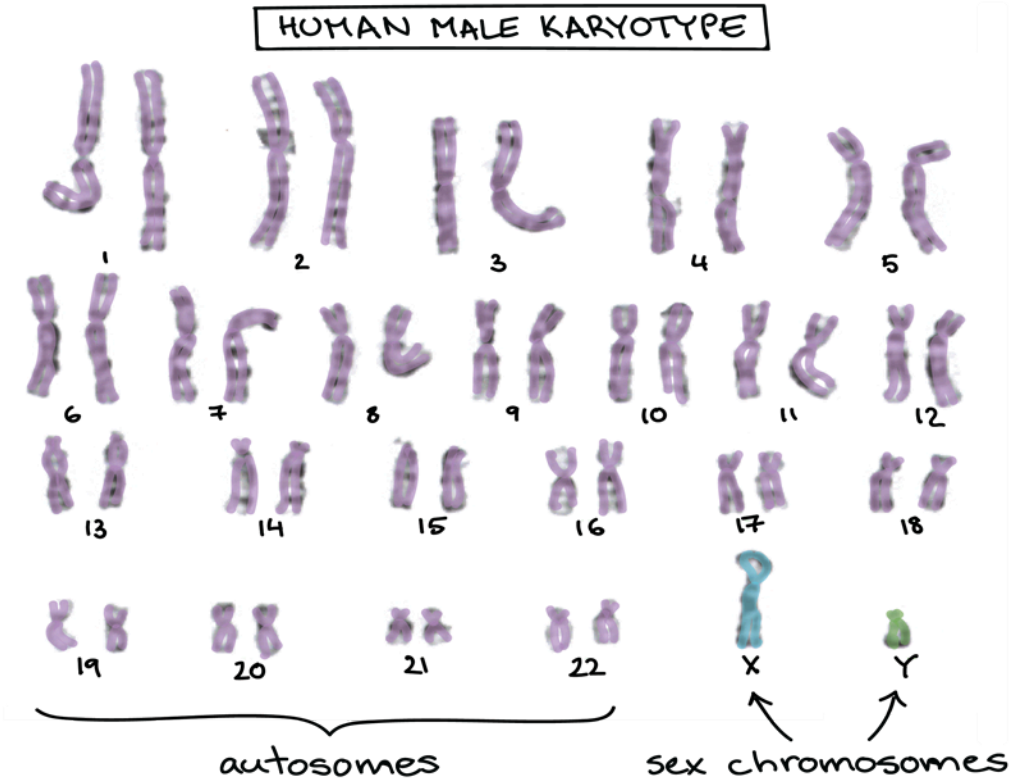
X-linked inheritance

Sex chromosomes and sex-linked inheritance

Most animals and many plants show sexual dimorphism; in other words, an individual can be either male or female. In most of these cases, sex is determined by special sex chromosomes. In these organisms, there are two categories of chromosomes, **sex chromosomes** and **autosomes** (the chromosomes other than the sex chromosomes). The rules of inheritance considered so far, with the use of Mendel's analysis as an example, are the rules of autosomes. Most of the chromosomes in a genome are autosomes. The sex chromosomes are fewer in number, and, generally in diploid organisms, there is just one pair.



Let us look at the human situation as an example. Human body cells have 46 chromosomes: 22 homologous pairs of autosomes plus 2 sex chromosomes. In females, there is a pair of identical sex chromosomes called the X chromosomes. In males, there is a non-identical pair, consisting of one X and one Y. The Y chromosome is considerably shorter than the X. At meiosis in females, the two X chromosomes pair and segregate like autosomes so that each egg receives one X chromosome. Hence the female is said to be the homogametic sex. At meiosis in males, the X and the Y pair over a short region, which ensures that the X and Y separate so that half the sperm cells receive X and the other half receive Y. Therefore the male is called the heterogametic sex.

Chromosomal Determination of Sex in Drosophila and Humans

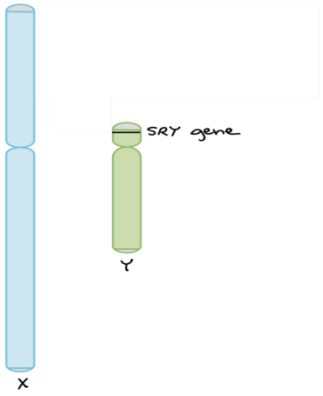
SEX CHROMOSOMES

Species	**XX**	**XY**	**XXY**	**XO**
Drosophila	♀	♂	♀	♂
Human	♀	♂	♂	♀

Sex chromosomes in humans

Human X and Y chromosomes determine the biological sex of a person, with XX specifying female and XY specifying male. Although the Y chromosome contains a small region of similarity to the X chromosome so that they can pair during meiosis, the Y chromosome is much shorter and contains many fewer genes.

To put some numbers to it, the X chromosome has about 800- 900 protein-coding genes with a wide variety of functions, while the Y chromosome has just 60- 70 protein-coding genes, about half of which are active only in the testes (sperm-producing organs).



The human Y chromosome plays a key role in determining the sex of a developing embryo. This is mostly due to a gene called SRY (“sex-determining region of Y”). SRY is found on the Y chromosome and encodes a protein that turns on other genes required for male development.

XX embryos don't have SRY, so they develop as female.

XY embryos do have SRY, so they develop as male.

In rare cases, errors during meiosis may transfer SRY from the Y chromosome to the X chromosome. If an SRY-bearing X chromosome fertilizes a normal egg, it will produce a chromosomally female (XX) embryo that develops as a male.

If an SRY-deficient Y chromosome fertilizes a normal egg, it will produce a chromosomally male embryo (XY) that develops as a female i.e., lost the characters of maleness.

Sex Chromosomes in Drosophila

The fruit fly Drosophila melanogaster has been one of the most important research organisms in genetics; its short, simple life cycle contributes to its usefulness in this regard (Figure 2-11). Fruit flies also have XX females and XY males. However, the mechanism of sex determination in Drosophila differs from that in mammals. In Drosophila, the number of X chromosomes determines sex: two X's result in a female and one X results in a male. In mammals, the presence of the Y determines maleness and the absence of a Y determines femaleness. This difference is demonstrated by the sexes of the abnormal chromosome types XXY and XO.

Cytogeneticists have divided the X and Y chromosomes of some species into homologous and non-homologous regions. The latter are called differential regions (Figure 2-13). These differential regions contain genes that have no counterparts on the other sex chromosome. Genes in the differential regions are said to be hemizygous ("half zygous") in males. Genes in the differential region of the X show an inheritance pattern called X linkage; those in the differential region of the Y show Y linkage. Genes in the homologous region show what might be called X-and-Y linkage. In general, genes on sex chromosomes are said to show sex linkage.

The genes on the differential regions of the sex chromosomes show patterns of inheritance related to sex. The inheritance patterns of genes on the autosomes produce male and female progeny in the same phenotypic proportions, as typified by Mendel's data (for example, both sexes might show a 3:1 ratio). However, crosses following the inheritance of genes on the sex chromosomes often show male and female progeny with different phenotypic ratios. In fact, for studies of genes of unknown chromosomal location, this pattern is a diagnostic of location on the sex chromosomes.

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.

Inheritance of X-linked genes

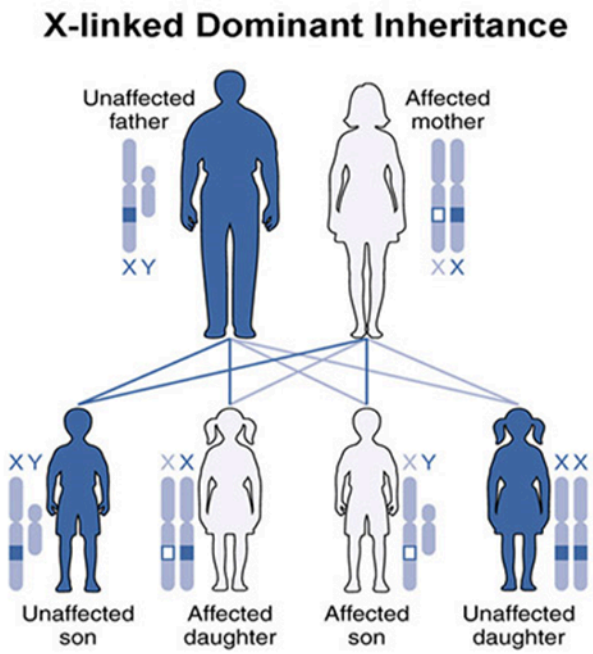
In Mendelian pattern of inheritance, the genes for contrasting characters were located on autosomes but not on the sex chromosomes. Secondly, the result of reciprocal cross is same as normal cross which is not the case with sex linked inheritance. There are three types of sex-linked genes depending upon their association with particular chromosome.

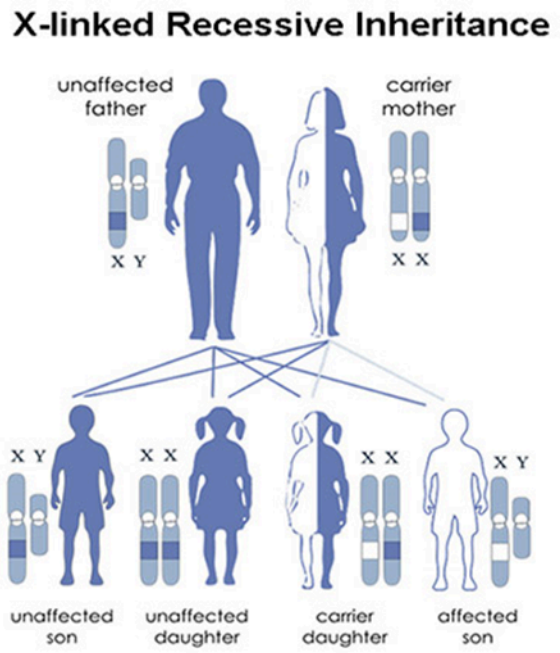
They are as follows:

(i) The genes which are located on X-chromosomes are called X-linked genes or sex linked genes.

(ii) The genes which are located on Y chromosomes are called Y-linked genes or holandric genes.

(iii) Certain genes are found to occur in both X and Y chromosomes. Such genes are called incomplete sex-linked genes.





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

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.

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 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 P_1 male parent (father) to F_2 male progeny (grandsons) through its F_1 heterozygous females (daughters), which are called carriers) and different F_1 and F_2 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., $X^A X^a \times X^a Y$), 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 F_1 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: 1. X-linked genetic disorders 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 F_1 flies were all red-eyed. F_2 generation of it included 3: 1 ratio of red and white-eyed flies. But all white eyed flies of F_2 generation were males only. When normal female of F_1 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.

In order to understand the inheritance of character present in sex chromosomes, let us understand transmission of X-chromosome from male individual in Drosophila

When a gene is present on the X chromosome, but not on the Y chromosome, it is said to be X-linked. X-linked genes have different inheritance patterns than genes on non-sex chromosomes (autosomes). That's because these genes are present in different copy numbers in males and females.

Since a female has two X chromosomes, she will have two copies of each X-linked gene. For instance, in the fruit fly Drosophila (which, like humans, has XX females and XY males), there is a eye color gene called white that's found on the X chromosome, and a female

fly will have two copies of this gene. If the gene comes in two different alleles, such as X^W (dominant, normal red eyes) and X^w (recessive, white eyes), the female fly may have any of three genotypes: X^WX^W (red eyes), $X^W X^w$ (red eyes), and X^wX^w (white eyes).

However, because the gene is X-linked, and because it was the female parent who had the recessive phenotype (white eyes), all the male offspring—who get their only X from their mother—have white eyes (X^w Y). All the female offspring have red eyes because they received two X's, with the X^W from the father concealing the recessive X^w from the mother.

A male has different genotype possibilities than a female. Since he has only one X chromosome (paired with a Y), he will have only one copy of any X-linked genes. For instance, in the fly eye color example, the two genotypes a male can have are: X^W Y (red eyes) and X^w Y (white eyes). Whatever allele the male fly inherits for an X-linked gene will determine his appearance, because he has no other gene copy—even if the allele is recessive in females, rather than homozygous or heterozygous, males are said to be hemizygous for X-linked genes.

We can see how sex linkage affects inheritance patterns by considering a cross between two flies, a white-eyed female (X^w X^w) and a red-eyed male (X^W Y). If this gene were on a non-sex chromosome, or autosome, we would expect all of the offspring to be red-eyed, because the red allele is dominant to the white allele. What we actually see is the following:

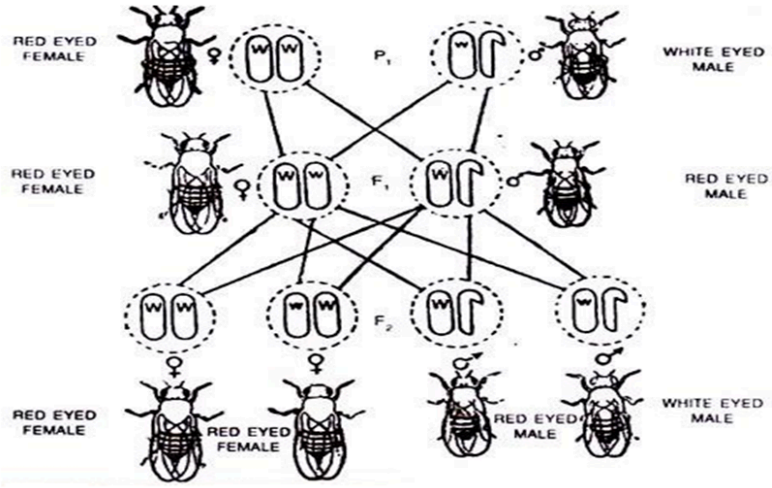
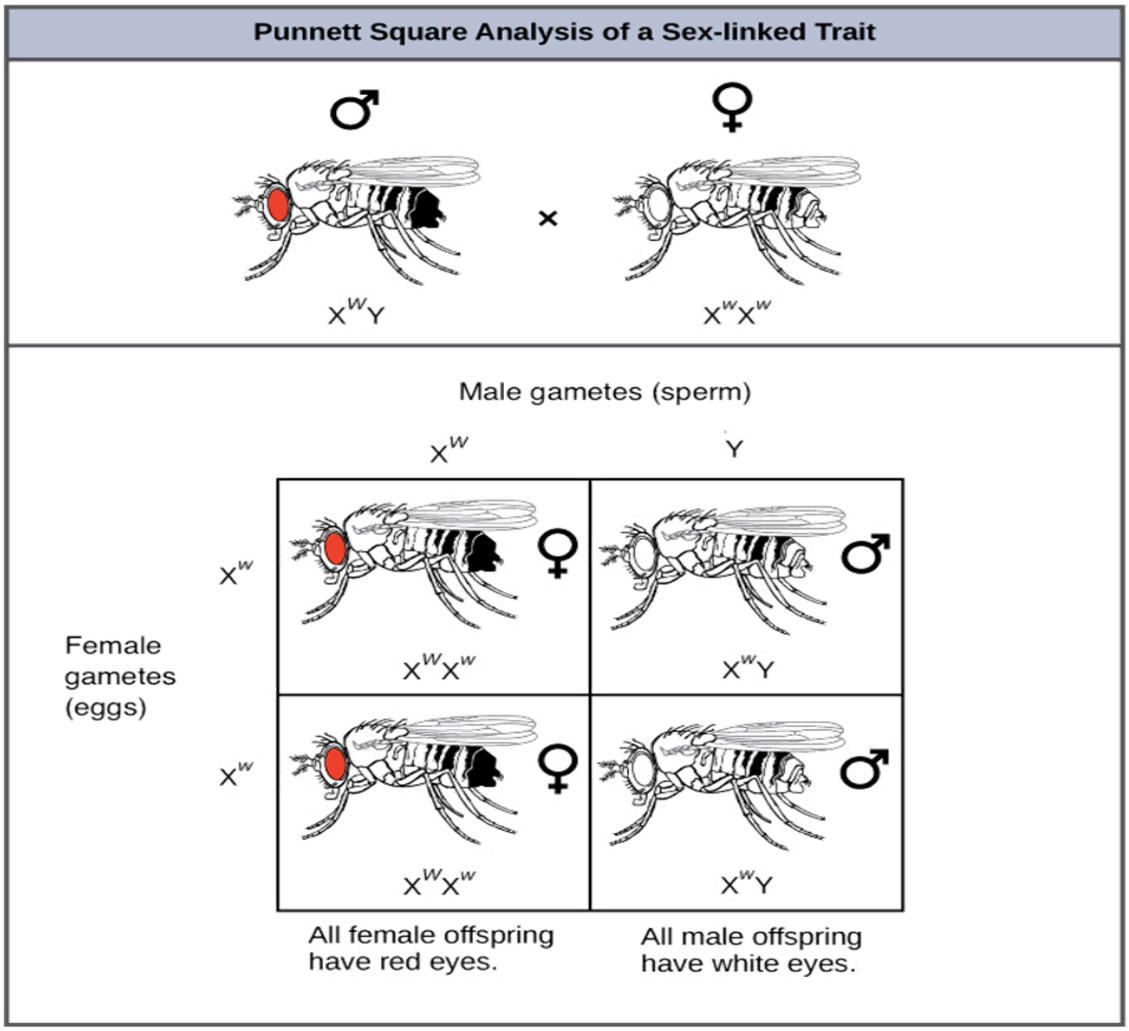


Fig. 5.17 Sex-Linked Inheritance in Drosophila. Cross between Red-Eyed Female and White-Eyed Male



Let's look at an example from Drosophila. The wild-type eye color of Drosophila is dull red, but pure lines with white eyes are available. This phenotypic difference is determined by two alleles of a gene located on the differential region of the X chromosome. When white-eyed males are crossed with red-eyed females, all the F_1 progeny have red eyes, showing that the allele for white is recessive. Crossing the red-eyed F_1 males and females produces a 3:1 F_2 ratio of red-eyed to white-eyed flies, but all the white-eyed flies are males. This inheritance pattern is explained by the alleles being located on the differential region of the X chromosome; in other words, by X-linkage. The genotypes are shown in Figure. The reciprocal cross gives a different result. A reciprocal cross between white-eyed females and red-eyed males gives an F_1 in which all the females are red eyed, but all the males are white eyed. The F_2 consists of one-half red-eyed and one-half white-eyed flies of both sexes. Hence in sex linkage, we see examples not only of different ratios in different sexes, but also of differences between reciprocal crosses.

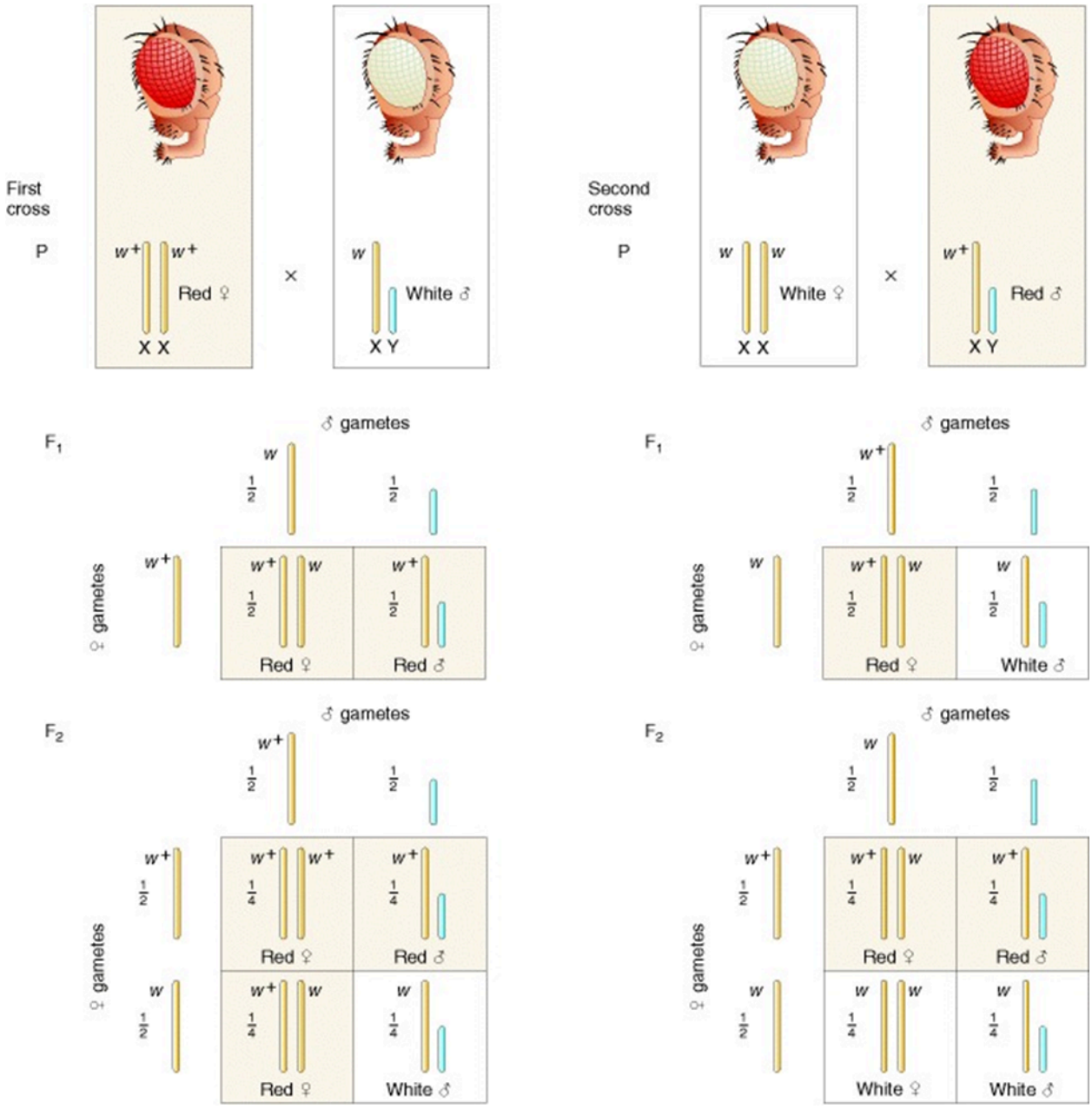


Figure. Explanation of the different results from reciprocal crosses between red-eyed (red) and white-eyed (white) Drosophila. (In Drosophila and many other experimental systems, a superscript plus sign is used to designate the normal, or wild-type allele. Here w + = red and w = white.)

In Drosophila, eye color has nothing to do with sex determination, so we see that genes on the sex chromosomes are not necessarily related to sexual function. The same is true in humans, for whom pedigree analysis has revealed many X-linked genes, of which few could be construed as being connected to sexual function.

2. X-linked genetic disorders in Human

The chromosomes present in the diploid cells of the majority of the sexually reproducing animals are of two types: autosomes bearing genes for somatic characters and sex chromosomes bearing genes for sex.

Such genes which are always associated with sex chromosomes are called sex-linked genes. In man and Drosophila the sex chromosomes (X and Y) are unequal in size and shape, X being larger and rod shaped whereas Y is small and slightly curved. In birds and butterflies the sex chromosomes (Z and W) are also unequal in shape and size, Z being larger than W.

The common sex-linked disorders that are mostly found in humans are mostly recessive. Sex chromosomes also carry some genes for non-sexual characters such as **colour blindness** and **haemophilia.**

They include disorders like Color-blindness, Haemophilia , etc.

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)

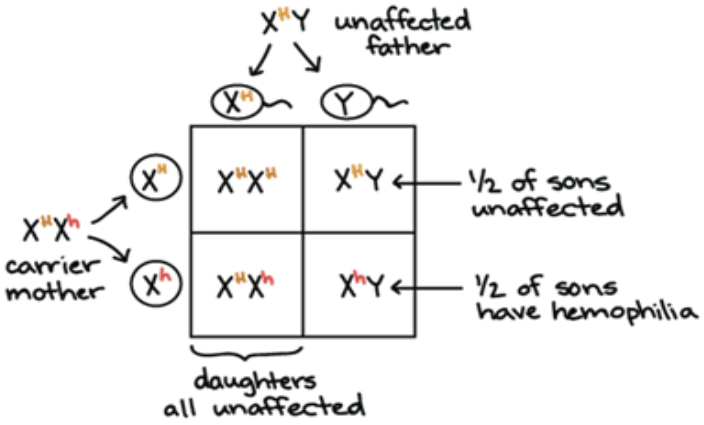
The same principles we see at work in fruit flies can be applied to human genetics. In humans, the alleles for certain conditions (including some forms of color blindness, hemophilia,) are X-linked. These diseases are much more common in men than they are in women due to their X-linked inheritance pattern.

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.

Let's explore this using an example in which a mother is heterozygous for a disease-causing allele. Women who are heterozygous for disease alleles are said to be carriers, and they usually don't display any symptoms themselves. Sons of these women have a 50% chance of getting the disorder, but daughters have little chance of getting the disorder (unless the father also has it), and will instead have a 50% chance of being carriers.

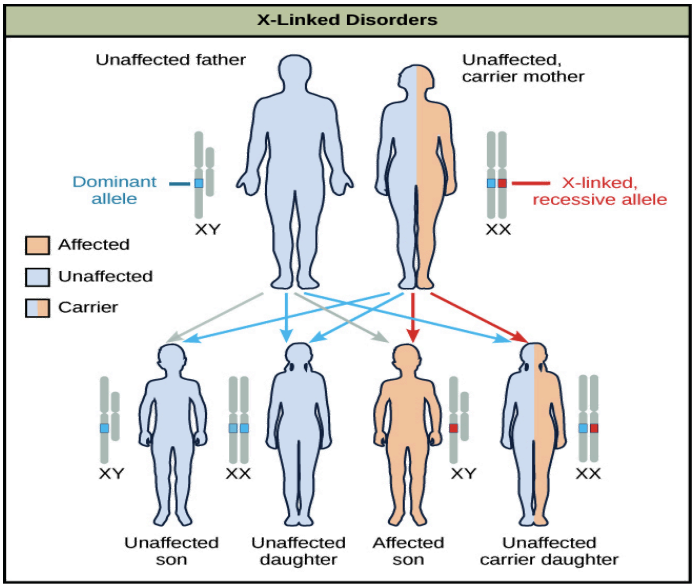
Recessive X-linked traits appear more often in males than females because, if a male receives a "bad" allele from his mother, he has no chance of getting a "good" allele from his father (who provides a Y) to hide the bad one. Females, on the other hand, will often receive a normal allele from their fathers, preventing the disease allele from being expressed.

Let's look at a Punnett square example using an X-linked human disorder: hemophilia, a recessive condition in which a person's blood does not clot properly. A person with hemophilia may have severe, even life-threatening, bleeding from just a small cut.



Hemophilia is caused by a mutation in either of two genes, both of which are located on the X chromosome. Both genes encode proteins that help blood clot14. Let's focus on just one of these genes, calling the functional allele XH and the disease allele Xh.

In our example, a woman who is heterozygous for normal and hemophilia alleles (XH Xh) has children with a man who is hemizygous for the normal form (XH Y). Both parents have normal blood clotting, but the mother is a carrier. What is the chance of their sons and daughters having hemophilia?



Since the mother is a carrier, she will pass on the hemophilia allele (X^h) on to half of her children, both boys and girls.

None of the daughters will have hemophilia (zero chance of the disorder). That's because, in order to have the disorder, they must get a X^h allele from both their mother and their father. There is 0 chance of the daughters getting an X^h allele from their father, so their overall chance of having hemophilia is zero.

The sons get a Y from their father instead of an X, so their only copy of the blood clotting gene comes from their mother. The mother is heterozygous, so half of the sons, on average, will get an X^h allele and have hemophilia (1/ 2 chance of the disorder).

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