4.6: Sex-Linkage and sex determination

In the previous chapter we introduced sex chromosomes and autosomes. For loci on autosomes, the alleles follow the normal Mendelian pattern of inheritance. However, for loci on the sex chromosomes this is mostly not true, because most of the loci on the typical X-chromosome are absent from the Y-chromosome, even though they act as a homologous pair during meiosis. Instead, they will follow a sex-linked pattern of inheritance.

X-Linked Genes: the white gene in *Drosophila melanogaster*

A well-studied sex-linked gene is the white gene on the X chromosome of *Drosophila melanogaster*. Normally flies have red eyes but flies with a mutant allele of this gene called *white*\(^{-}\) (\(w^{-}\)) have white eyes because the red pigments are absent. Because this mutation is recessive to the wild type \(w^{+}\) allele females that are heterozygous have normal red eyes. Female flies that are homozygous for the mutant allele have white eyes. Because there is no white gene on the Y chromosome, male flies can only be hemizygous for the wild type allele or the mutant allele.

Note about nomenclature

In genetics, genes are often named after their mutant (usually but not always loss-of-function) phenotypes. Remember, that genetics has its origin in observing phenotypes. The white allele described here was identified in 1910 (Morgan, T.H.) - long before gene sequences could be determined. The DNA sequence of this locus was not published until 1984 (O'Hare et al). We know now that this gene encodes a transporter protein that deposits pigment and that the mutant allele does not produce a functional transporter, but the gene name white continues to be used.

The process of identifying mutant phenotypes and then later determining which gene is involved is called forward genetics.
The alternative, to identify a candidate gene and manipulate it to observe the phenotype, is called reverse genetics, and was only made possible by the advent of modern molecular biology tools.

![Genotype and Phenotype](image)

**Figure 1**: Relationship between genotype and phenotype for a the white gene on the X-linked gene in *Drosophila melanogaster*. The Y chromosome is indicated with a capital Y because it does not have a copy of the white gene. (Original-Harrington/Locke-CC:AN)

A researcher may not know beforehand whether a novel mutation is sex-linked. The definitive method to test for sex-linkage is reciprocal crosses (Figure 3.10). This means to cross a male and a female that have different phenotypes, and then conduct a second set of crosses, in which the phenotypes are reversed relative to the sex of the parents in the first cross. For example, if you were to set up reciprocal crosses with flies from pure-breeding $w^+$ and $w^-$ strains the results would be as shown in Figure 3.10. Whenever reciprocal crosses give different results in the F1 and F2 and whenever the male and female offspring have different phenotypes the usual explanation is sex-linkage. Remember, if the locus were autosomal the F1 and F2 progeny would be different from either of these crosses.

A similar pattern of sex-linked inheritance is seen for X-chromosome loci in other species with an XX-XY sex chromosome system, including mammals and humans. The ZZ-ZW system is similar, but reversed (see below).

![Reciprocal Crosses](image)

**Figure 2**: Reciprocal crosses involving an X-linked gene in *Drosophila melanogaster*. In the first cross (left) all of the offspring have red eyes. In second (reciprocal) cross (right) all of the female offspring have red eyes and the male offspring all have white eyes. If the F1 progeny are crossed (to make the P2), the F2 progeny will be different in each cross. The first cross has all red-eyed females and half red-eyed males. The reciprocal cross has half red-eyed males and females. Thomas Morgan won the Nobel Prize for using these crosses to demonstrate that genes (such as white) were on chromosomes (in this case the X-chromosome). (Wikipedia-PAR-PD)
Sex Determination in animals.

There are various mechanisms for sex determination in animals. These include sex chromosomes, chromosome dosage, and environment.

For example in humans and other mammals XY embryos develop as males while XX embryos become females. This difference in development is due to the presence of only a single gene, the SRY gene, on the Y-chromosome. Its presence and expression dictates that the sex of the individual will be male. Its absence results in a female phenotype.

Although Drosophila melanogaster also has an XX-XY sex chromosomes, its sex determination system uses a different method, that of X:Autosome (X:A) ratio. In this system it is the ratio of autosome chromosome sets (A) relative to the number of X-chromosomes (X) that determines the sex. Individuals with two autosome sets and two X-chromosomes (2A:2X) will develop as females, while those with only one X-chromosome (2A:1X) will develop as males. The presence/absence of the Y-chromosome and its genes are not significant.

In other species of animals the number of chromosome sets can determine sex. For example the haploid-diploid system is used in bees, ants, and wasps. Typically haploids are male and diploids are female.

In other species, the environment can determine an individual's sex. In alligators (and some other reptiles) the temperature of development dictates the sex, while in many reef fish, the population sex ratio can cause some individuals to change sex.

Dosage Compensation for Loci on Sex Chromosomes.

Mammals and Drosophila both have XX - XY sex determination systems. However, because these systems evolved independently they work differently with regard to compensating for the difference in gene dosage (and sex determination – see above). Remember, in most cases the sex chromosomes act as a homologous pair even though the Y-chromosome has lost most of the loci when compared to the X-chromosome. Typically, the X and the Y chromosomes were once similar but, for unclear reasons, the Y chromosomes have degenerated, slowly mutating and loosing its loci. In modern day mammals the Y chromosomes have very few genes left while the X chromosomes remain as they were. This is a general feature of all organisms that use chromosome based sex determination systems. Chromosomes found in both sexes (the X or the Z) have retained their genes while the chromosome found in only one sex (the Y or the W) have lost most of their genes. In either case there is a gene dosage difference between the sexes: e.g. XX females have two doses of X-chromosome genes while XY males only have one. This gene dosage needs to be compensated in a process called dosage compensation. There are two major mechanisms.

In Drosophila and many other insects, to make up for the males only having a single X chromosome the genes on it are expressed at twice the normal rate. This mechanism of dosage compensation restores a balance between proteins encoded by X-linked genes and those made by autosomal genes.

In mammals a different mechanism is used, called X-chromosome inactivation.
X-chromosome Inactivation in Mammals

In mammals the dosage compensation system operates in females, not males. In XX embryos one X in each cell is randomly chosen and marked for inactivation. From this point forward this chromosome will be inactive, hence its name X\text{inactive} (X_i). The other X chromosome, the X\text{active} (X_a), is unaffected. The X_i is replicated during S phase and transmitted during mitosis the same as any other chromosome but most of its genes are never allowed to turn on. The chromosome appears as a condensed mass within interphase nuclei called the Barr body. With the inactivation of genes on one X-chromosome, females have the same number of functioning X-linked genes as males.

This random inactivation of one X-chromosome leads to a commonly observe phenomenon in cats. A familiar X-linked gene is the Orange gene (O) in cats. The O^O allele encodes an enzyme that results in orange pigment for the hair. The O^B allele causes the hairs to be black. Heterozygous females have an orange and black mottled phenotype known as tortoiseshell. This is due to patches of skin cells having different X-chromosomes inactivated. In each orange hair the X_i chromosome carrying the O^B allele is inactivated. The O^O allele on the X_a is functional and orange pigments are made. In black hairs the reverse is true, the X_i chromosome with the O^O allele is inactive and the X_a chromosome with the O^B allele is active. Because the inactivation decision happens early during embryogenesis, the cells continue to divide to make large patches on the adult cat skin where one or the other X is inactivated.

![Genotype and Phenotype Chart](https://bio.libretexts.org/Courses/University_of_Arkansas_Little_Rock/BIOL3300_Genetics/04%3A_Inheritance/4.06%3A__Se...

**Figure**: Relationship between genotype and phenotype for an X-linked gene in cats. The O^O allele = orange while the O^B allele = black. (Original-Harrington-CC:AN)

The Orange gene in cats is a good demonstration of how the mammalian dosage compensation system affects gene expression. However, most X-linked genes do not produce such dramatic mosaic phenotypes in heterozygous females. A more typical example is the F8 gene in humans. It makes Factor VIII blood clotting proteins in liver cells. If a male is hemizygous for a mutant allele the result is hemophilia type A. Females homozygous for mutant alleles will also have hemophilia. Heterozygous females, those people who are \( F8^+/F8^- \), do not have hemophilia because even though half of their liver cells do not make Factor VIII (because the X with the \( F8^+ \) allele is inactive) the other 50% can. Because some of their liver cells are exporting Factor VIII proteins into the blood stream they have the ability to form blood clots throughout their bodies. The genetic mosaicism in the cells of their bodies does not produce a visible mosaic phenotype.
Females heterozygous for an F8 mutation have a mixture of liver cells in which the $F8^+$ or $F8^-$ chromosome is inactivated. Because people with the $F8^+/F8^-$ genotype have the same phenotype, normal blood clotting, as $F8^+/F8^+$ people the $F8^-$ mutation is classified as recessive. (Original-Harrington/Locke-CC:AN)

Other Sex-Linked Genes – Z-linked genes

One last example is a Z-linked gene that influences feather colour in turkeys. Turkeys are birds, which use the ZZ-ZW sex chromosome system. The $E$ allele makes the feathers bronze and the $e$ allele makes the feathers brown (Figure 3.13). Only male turkeys can be heterozygous for this locus, because they have two Z chromosomes. They are also uniformly bronze because the $E$ allele is completely dominant to the $e$ allele and birds use a dosage compensation system similar to Drosophila and not mammals. Reciprocal crosses between turkeys from pure-breeding bronze and brown breeds would reveal that this gene is in fact Z-linked.

![Figure](https://bio.libretexts.org/Courses/University_of_Arkansas_Little_Rock/BIOL3300_Genetics/04%3A_Inheritance/4.06%3A__Se…)

**Figure (Page Index[5]):** Relationship between genotype and phenotype for a Z-linked gene in turkeys. The W chromosome does not have an $E/e$-gene so it is just indicated with a capital W. (Original-Harrington/Locke-CC:AN)