3.5: Sex-Linkage- An Exception to Mendel’s First Law

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.

![Figure 9: Relationship between genotype and phenotype for a the white gene on the X-linked gene in Drosophila melanogaster.](https://bio.libretexts.org/Bookshelves/Genetics/Book%3A_Online_Open_Genetics_(Nickle_and_Barrette-Ng)/03%3A_Genetic...)
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 (PagIndex{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).

![Figure](https://bio.libretexts.org/Bookshelves/Genetics/Book%3A_Online_Open_Genetics_(Nickle_and_Barrette-Ng)/03%3A_Genetic…)

**Figure (PagIndex{10})**: 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)

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**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 TDF-Y 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 losing 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\_inactive (X\_i). The other X chromosome, the X\_active (X\_a), is unaffected. The Xi 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. The phenotypes of various genotypes of cats are shown in Figure \(\PageIndex{11}\). Note that the 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 Xi 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 Xi 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.
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 (Figure \(\PageIndex{12}\)). 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.

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 \(\PageIndex{13}\)). 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 \textit{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.

![Genotype and phenotype diagram](https://bio.libretexts.org/Bookshelves/Genetics/Book%3A_Online_Open_Genetics_(Nickle_and_Barrette-Ng)/03%3A_Genetics-Fundamentals/03-03-Mechanisms_of_Sex_Determination_Systems/10-Mechanisms_of_Sex_Determination_Systems)

Figure \( \PageIndex{13} \): 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-Harringtion/Locke-CC:AN)

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### Mechanisms of Sex Determination Systems

Sex is a phenotype. Typically, in most species, there are multiple characteristics, in addition to sex organs, that distinguish male from female individuals (although some species are normally \textit{hermaphrodites} where both sex organs are present in the same individual). The morphology and physiology of male and females is a phenotype just like hair or eye colour or wing shape. The sex of an organism is part of its phenotype and can be genetically (or environmentally) determined.

For each species, the genetic determination relies on one of several gene or chromosome based mechanisms. See Figure \( \PageIndex{14} \) for a summary. There are, for other species, also a variety of environmental mechanisms, too (rearing temperature, social interactions, \textit{parthenogenesis}). Whatever the sex choice mechanism, however, there are two different means by which the cells of an organism carry out this decision: \textit{hormonal} or \textit{cell-autonomous}.
Different types of chromosomal based sex determination

From top to bottom, there is the archetypal XX/XY system found in humans (and most mammals) with the TDF-Y gene leading to a male phenotype; the ZW/ZZ system found in chickens (birds, moths, and butterflies); the same XX/XY system in Drosophila (sex is determined by the X-chromosome:autosome ratio); the XX/XO system as found in grasshoppers; and the diploid/haploid system as found in bees (and ants, and wasps). Also, the hormonal mechanism is used in humans, while all the other examples use the cell-autonomous mechanism for development of the male or female sex phenotype.

Hormonal mechanism: With this system, used by mammals for example, including humans, the zygote initially develops into a sexually undifferentiated embryo that can become either sex. Then, depending on the sex choice of the genital ridge cells, they will grow and differentiate into male (testis) or female (ovary) gonads, which will then produce the appropriate hormones (e.g. testosterone or estrogen). This hormone will circulate throughout the body and cause all the other tissues to develop and differentiate accordingly, into a male or female phenotype for that individual. Thus, the circulating hormone “tells” all the cells and tissues what sex to be and which sexual phenotype to be.

A freemartin is a type of chimera found in cattle (and some other mammals). Externally it appears as a female but is infertile, and has masculinized behavior and non-functioning ovaries. The animal originates as a female (XX), but
acquires male (XY) cells or tissues in utero by exchange of some cellular material from a male twin. The female reproductive development is altered by anti-Müllerian hormone from the male twin, acquired via vascular connections between placentas.

**Cell-autonomous mechanism:** With this system, used by many animals, including birds and insects, the zygote cell initially has a sex phenotype set at the cell level. All cells intrinsically know, individually, which sex they are and develop accordingly, giving the appropriate sexual characteristics and phenotype. Each cell is autonomous with respect to its sex; there are no sex hormone cues to determine the sex expressed. This autonomy can lead to sexual gynandromorphs, which are mosaics that display both male and female characteristics in a mosaic fashion, typically split down the midline of the organism. These rare individuals are thought to be the result of an improper sex chromosome segregation that occurs in a cell very early in development so that one half of the individual has cells with a male chromosome set while the other half has cells with a female set. If the species is sexually dimorphic (external morphology easily distinguishes males from females) they are easily visible and are even sometimes seen in the wild. See Figure \(\PageIndex{15}\) for a local example. A search on the internet will bring up many more examples.

![Figure \(\PageIndex{15}\): – Drosophila sexual gynadromorph. The left side is female with the most distal abdominal segments being not heavily pigmented, while the right is male and the two most distal segments are heavily pigmented (arrow). This example was found by a U. of Alberta student in the GENET 375 lab course, Introductions to Molecular Genetic Techniques. (Original – Locke – CC:AN)](https://bio.libretexts.org/Bookshelves/Genetics/Book%3A_Online_Open_Genetics_(Nickle_and_Barrette-Ng)/03%3A_Genetic…)

While gynandromorphs are seen in cell-autonomous species, such as insects and birds, they are not seen in hormonally determined species, such as mammals, because all the cells display the same sex phenotype caused by the circulating sex hormones. Sexual gynandromorphs appear to be absent in reptiles, amphibians, and fish indicating that they don’t use a cell-autonomous mechanism. Nevertheless, there are genetic mosaic individuals in these groups but they do not appear to involve sex determined traits, which is required for a true gynandromorph. They often involve mosaicism of alleles at a single gene locus that affect external morphology (e.g. color).

- A **gynandromorph** is an organism that made up of mosaic tissues of male and female genotypes and displays both male and female characteristics.
- A **mosaic** is an organism or a tissue that contains two or more types of genetically different cells derived from the...
same zygote.

- A chimera is a single organism composed of genetically distinct cells derived from different zygotes.