Sex Determination- Sex Linked, Sex Influenced and Sex Limited Traits

In Biological world, a wide array of reproductive modes are known such as asexual, sexual, alternation of generation. Some organisms solely rely on sexual reproduction while in others it is short period of sexual reproduction followed with prolonged periods of asexual reproduction. Orderly transmission of genetic material from parents to offspring, and the resultant phenotypic variability, relies on the processes of segregation and independent assortment that occur during meiosis. Meiosis produces haploid gametes so that, following fertilization, the resulting offspring maintain the diploid number of chromosomes characteristic of their kind. Thus, meiosis ensures genetic constancy within members of the same species.

These events, seen in the perpetuation of all sexually reproducing organisms, depend ultimately on an efficient union of gametes during fertilization. In turn, successful fertilization depends on some form of sexual differentiation in the reproductive organisms.

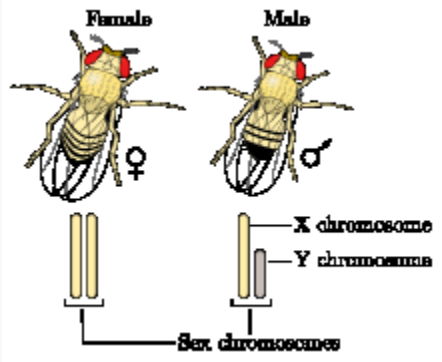
In many animal species, including humans, the differentiation of the sexes is more evident as phenotypic dimorphism of males and females. The ancient symbol for iron and for Mars, depicting a shield and spear ({), and the ancient symbol for copper and for Venus, depicting a mirror (+), have also come to symbolize maleness and femaleness, respectively.

Dissimilar or heteromorphic chromosomes, such as the XY pair in mammals, characterize one sex or the other in a wide range of species, resulting in their label as sex chromosomes. Nevertheless, in many species, genes rather than chromosomes ultimately serve as the underlying basis of sex determination.

Sexual dimorphism (differences between males and females) in multicellular animals, biologists distinguish between **primary sexual differentiation**, which involves only the gonads, where gametes are produced, and **secondary sexual differentiation**, which involves the overall appearance of the organism, including clear differences in such organs as mammary glands and external genitalia as well as in nonreproductive organs. In plants and animals, the terms unisexual, dioecious, and gonochoricare equivalent; they all refer to an individual containing only male or only female reproductive organs. Conversely, the terms bisexual, monoecious, and hermaphroditic refer to individuals con-taining both male and female reproductive organs, a common occurrence in both the plant and animal kingdoms. These organisms can produce both eggs and sperm. The term intersexis usually reserved for individuals of an inter-mediate sexual condition, most of whom are sterile.

Sex Determination

XX/XY sex chromosomes



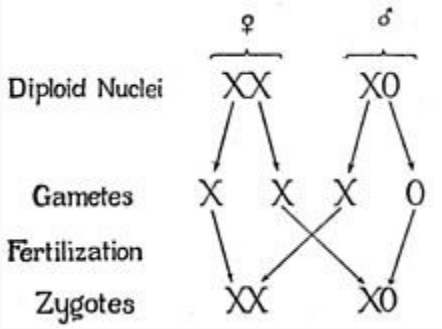
Drosophila sex-chromosomes

Main article: XY sex-determination system

The **XX/XY sex-determination system** is the most familiar, as it is found in humans. In the system, females have two of the same kind of sex chromosome (XX), while males have two distinct sex chromosomes (XY). The XY sex chromosomes are different in shape and size from each other, unlike the autosomes, and are termed allosomes. Some species (including humans) have a gene SRY on the Y chromosome that determines maleness; others (such as the fruit fly) use the presence of two X chromosomes to determine femaleness.[11] Because the fruit fly, as well as other species, use the number of Xs to determine sex, they are nonviable with an extra X. SRY-reliant species can have conditions such as XXY and still live.[12] Human sex is determined by containing SRY or not. Once SRY is activated, cells create testosterone and anti-müllerian hormone to turn the genderless sex organs into male.[12] With females, their cells excrete estrogen, driving the body down the female pathway. Not all organisms remain gender indifferent for a time after they're created; for example, fruit flies differentiate into specific sexes as soon as the egg is fertilized.[12] In Y-centered sex determination, the SRY gene is not the only gene to have an influence on sex. Despite the fact that SRY seems to be the main gene in determining male characteristics, it requires the action of multiple genes to develop testes. In XY mice, lack of the gene DAX1 on the X chromosome results in sterility, but in humans it causes adrenal hypoplasia congenita.[13] However, when an extra DAX1 gene is placed on the X, the result is a female, despite the existence of SRY.[14] Also, even when there are normal sex chromosomes in XX females, duplication or expression of SOX9 causes testes to develop.[15][16] Gradual sex reversal in developed mice can also occur when the gene FOXL2 is removed from females.[17] Even though the gene DMRT1 is used by birds as their sex locus, species who have XY chromosomes also rely upon DMRT1, contained on chromosome 9, for sexual differentiation at some point in their formation.[12]

The XX/XY system is also found in most other mammals, as well as some insects. Some fish also have variants of this, as well as the regular system. For example, while it has an XY format, the *Xiphophorus variatus* also has a second Y chromosome, known as Y', that creates XY' females and YY' males.[10] At least one monotreme, the platypus, presents a particular sex determination scheme that in some ways resembles that of the ZW sex chromosomes of birds,

and also lacks the SRY gene, whereas some rodents, such as several Arvicolinae (voles and lemmings), are also noted for their unusual sex determination systems. The platypus has ten sex chromosomes; males have an XYXYXYXYXY pattern while females have ten X chromosomes. Although it is an XY system, the platypus' sex chromosomes share no homologues with eutherian sex chromosomes.[18] Instead, homologues with eutherian sex chromosomes lie on the platypus chromosome 6, which means that the eutherian sex chromosomes were autosomes at the time that the monotremes diverged from the therian mammals (marsupials and eutherian mammals). However, homologues to the avian DMRT1 gene on platypus sex chromosomes X3 and X5 suggest that it is possible the sex-determining gene for the platypus is the same one that is involved in bird sex-determination. More research must be conducted in order to determine the exact sex determining gene of the platypus.[19]



Heredity of sex chromosomes in XO sex determination

XX/X0 sex determination[edit]

Main article: X0 sex-determination system

In this variant of the XY system, females have two copies of the sex chromosome (XX) but males have only one (X0). The *0* denotes the absence of a second sex chromosome. Generally in this method, the sex is determined by amount of genes expressed across the two chromosomes. This system is observed in a number of insects, including the grasshoppers and crickets of order Orthoptera and in cockroaches (order Blattodea). A small number of mammals also lack a Y chromosome. These include the Amami spiny rat (*Tokudaia osimensis*) and the Tokunoshima spiny rat (*Tokudaia tokunoshimensis*) and *Sorex araneus*, a shrew species. Transcaucasian mole voles (*Ellobius lutescens*) also have a form of XO determination, in which both genders lack a second sex chromosome.[14] The mechanism of sex determination is not yet understood.[20]

The nematode *C. elegans* is male with one sex chromosome (X0); with a pair of chromosomes (XX) it is a hermaphrodite.[21] Its main sex gene is XOL, which encodes XOL-1 and also controls the expression of the genes TRA-2 and HER-1. These genes reduce male gene activation and increase it, respectively.[22]

ZW sex chromosomes[edit]

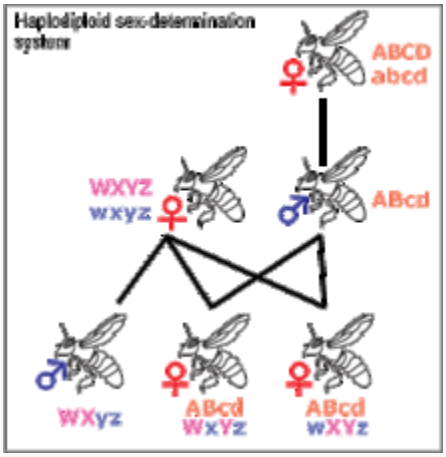
Main article: ZW sex-determination system

The **ZW sex-determination system** is found in birds, some reptiles, and some insects and other organisms. The ZW sex-determination system is reversed compared to the XY system: females

have two different kinds of chromosomes (ZW), and males have two of the same kind of chromosomes (ZZ). In the chicken, this was found to be dependent on the expression of DMRT1.[23] In birds, the genes FET1 and ASW are found on the W chromosome for females, similar to how the Y chromosome contains SRY.[12] However, not all species depend upon the W for their sex. For example, there are moths and butterflies that are ZW, but some have been found female with ZO, as well as female with ZZW.[21]Also, while mammals inactivate one of their extra X chromosomes when female, it appears that in the case of Lepidoptera, the males produce double the normal amount of enzymes, due to having two Z's.[21] Because the use of ZW sex determination is varied, it is still unknown how exactly most species determine their sex.[21] Despite the similarities between ZW and XY, the sex chromosomes do not line up correctly and evolved separately. In the case of the chicken, their Z chromosome is more similar to humans' autosome 9.[24] The chicken's Z chromosome also seems to be related to the X chromosomes of the platypus.[25] When a ZW species, such as the Komodo Dragon, reproduce parthenogenetically, males are usually only produced. This is due to the fact that the haploid eggs double their chromosomes, resulting in ZZ or WW. The ZZ become males, but the WW are not viable and are not brought to term.[26]

UV sex chromosomes

In some Bryophyte and some algae species, the gametophyte stage of the life cycle, rather than being hermaphrodite, occurs as separate male or female individuals that produce male and female gametes respectively. When meiosis occurs in the sporophyte generation of the life cycle, the sex chromosomes known as U and V assort in spores that carry either the U chromosome and give rise to female gametophytes, or the V chromosome and give rise to male gametophytes.[27]



Haplodiploid sex chromosomes

Haplodiploidy

Haplodiploidy is found in insects belonging to Hymenoptera, such as ants and bees. Unfertilized eggs develop into haploid individuals, which are the males. Diploid individuals are generally female but may be sterile males. Males cannot have sons or fathers. If a queen bee mates with one drone, her daughters share ¾ of their genes with each other, not ½ as in the XY and ZW

systems. This is believed to be significant for the development of eusociality, as it increases the significance of kin selection, but it is debated. Most females in the Hymenoptera order can decide the sex of their offspring by holding received sperm in their spermatheca and either releasing it into their oviduct or not. This allows them to create more workers, depending on the status of the colony.

Non-genetic sex-determination systems

All alligators determine sex of their offspring by the temperature of the nest.

Temperature-dependent sex determination

Many other sex-determination systems exist. In some species of reptiles, including alligators, some turtles, the tuatara, sex is determined by the temperature at which the egg is incubated during a temperature sensitive period. There are no examples of temperature-dependent sex determination (TSD) in birds (including megapodes, which had formerly been thought to exhibit this phenomenon, but actually exhibit temperature-dependent embryo mortality). For some species with TSD, sex determination is achieved by hotter temperatures being one sex and cooler temperatures being the other. For others, the extreme temperatures are one sex and the middle temperature is the other. These temperature thresholds are known as Pattern I and Pattern II, respectively. The temperatures required for the specific sexes are known as the female promoting temperature and the male promoting temperature.[31]When the temperature stays near the threshold during the temperature sensitive period, the sex ratio is varied between the two sexes.[32] Some species set their temperature standards based on when an enzyme is created. These species that rely upon temperature for their sex determination do not have the SRY gene, but have other genes such as DAX1, DMRT1, and SOX9 that are expressed or not expressed depending on the temperature.[31] Some species such as the Nile Tilapia, Australian skink lizard, and Australian dragon lizard have sex determined by chromosomes, but this can later be switched by the temperature of incubation.[10] These species seem to be in a transitional state of evolution.

It is unknown how exactly temperature sex determination evolved. It could have evolved through certain sexes being more suited to certain areas that fit the temperature requirements. For example, a warmer area could be more suitable for nesting, so more females are produced to increase the amount that nest next season. However, at this stage it's mostly hypotheses.[33]

Other sex-determination systems

Although temperature-dependent sex determination is relatively common, there are many other environmental systems. Some species, such as some snails, practice sex change: adults start out male, then become female (See also sex reversal). In tropical clown fish, the dominant individual in a group becomes female while the other ones are male, and bluehead wrasses (*Thalassoma bifasciatum*) are the reverse. In the marine worm (*Bonellia viridis*), larvae become males if they make physical contact with a female, and females if they end up on the bare sea floor. This is triggered by the presence of a chemical produced by the females, bonellin. Some species, however, have no sex-determination system. Hermaphrodites include the common earthworm and certain species of snails. A few species of fish, reptiles, and insects reproduce by parthenogenesis and are female altogether. There are some reptiles, such as the boa constrictor and komodo dragon that can reproduce sexually and asexually, depending if a mate is available.[34]

In some arthropods, sex is determined by infection, as when bacteria of the genus *Wolbachia* alter their sexuality; some species consist entirely of ZZ individuals, with sex determined by the presence of *Wolbachia*.

When Gender Matters:

Sex Linked, Sex Limited and Sex Influenced Traits

For most inherited traits, the gender of the bearer of the genes is immaterial. Characteristics like free earlobes, fur color, etc., generally operate the same in males as they do in females.

But there are exceptions. These fall into three primary categories.

Sex Linked Traits are traits whose loci are literally on the sex chromosomes, so their transmission from generation to generation is affected by the sex chromosome complement of the individual. In any species with non-homologous sex chromosomes, these traits can be significant.

The first demonstration of sex linkage was the white eye gene in *Drosophila*, the fruit fly which has become so important to the study of classical genetics. Normal fruit fly eye color is a dull brick red. Mutations in this gene cause the eyes to be white. The white allele is recessive, but it was quickly determined that the inheritance pattern for this gene was different from those of other genes being studied. In some kinds of matings, reciprocal crosses produced different

results, something which had never been observed to happen with other genes. Not only that, but in some kinds of matings, the results for the male offspring would be different from the results for the female offspring. For instance, if a white-eyed female was mated to a red-eyed male, all of the female offspring would be red eyed, but all of the male offspring would be white eyed.

It turned out that this particular eye color gene was literally located on the X chromosome. Since females have two X chromosomes and males have only one, genetic effects in the two genders are different. And since females contribute an X to each offspring, male or female, and males contribute X chromosomes only to female offspring, naturally transmission patterns were different in different kinds of matings.

"Linkage" refers to the physical connection that exists between genes whose loci are on the same chromosome. Genes on the X chromosome are all linked to each other—thus they are **X-linked**.

X-linked traits have a number of interesting aspects. First, because females possess two X chromosomes and males possess only one, X-linked recessive traits appear far more commonly in males than in females. This is clear from simple statistics. A male will show the X-linked recessive trait due to receiving only a single copy of the allele, because he has no second X chromosome to carry a dominant allele which might hide the recessive. Females must inherit the recessive trait **twice** to show it, just as they do for any other recessive trait. This is a much more unlikely outcome. This is the source of the misconception that only males can display X-linked traits like color blindness.

Another interesting observation about X-linked traits is that males always receive their X chromosomes from their mothers, so they also receive any X-linked traits from their mothers. Their fathers have no contribution for those genes (though, of course, they do for the genes on all of the other chromosomes). Daughters inherit one X from each parent. And of course, the one X they inherit from their fathers will be the only X he has.

There are also a very few genes which are **Y-linked** (or **holandric**). Y-linked genes are carried on the Y chromosome, and are thus passed directly from father to son. Every son has a copy of his father's Y chromosome. In any pedigree showing unbroken lines of male descent, all of the connected males have copies of the same Y chromosome, and thus share any Y-linked characteristics.

One final note about that very significant white-eyed *Drosophila* gene. In combination with a strange chromosomal anomaly called **attached-X**, this gene also produced the first direct evidence that genes were literally carried on chromosomes. Useful little gene.

Gender matters for a couple of other kinds of traits as well.

Sex limited traits are generally autosomal, meaning that they are not found on the X or Y chromosomes. The genes for these traits behave exactly the same way that any autosomal gene behaves. The difference here comes in the expression of the genes in the phenotype of the individual. Sex-limited traits are expressed in only one gender. The traits are generally associated with primary or secondary sexual characteristics, and thus are expressed only in the gender which utilizes those characteristics. For example, there are genes which influence how much milk a lactating mother produces when she's nursing a baby. These genes are carried by both males and females, but only females ever express them. Another example is the condition **cryptorchidism** (undescended testicles). In development, the primary sexual organs of males (testicles) and females (ovaries) develop from the same embryonic tissue. This tissue is located low in the abdomen, in roughly the same position ovaries are located in fully developed females. But in fully developed males, the testicles are not located in the abdomen. Late in development, they move from their abdominal position, through the inguinal canal into the scrotum, which is essentially a small skin bag which hangs outside the body. This voyage is important, because the temperature inside the abdomen is too high for the development of viable sperm. Cryptorchidism is a genetically determined condition in which one or both testicles fail to make this voyage, and remain in the abdomen. (This is generally surgically corrected very early, because not only is a cryptorchid male sterile, but the undescended testicles are at increased risk for testicular cancer). The genes for this condition are autosomal; males and females each carry two alleles. But only males can possible exhibit the condition, because only males show the **normal** condition for testicle behavior and position.

Sex influenced traits are also autosomal, meaning that their genes are not carried on the sex chromosomes. Again, what makes these traits unusual is the way they are expressed phenotypically. In this case, the difference is in the ways the two genders express the genes.

One classic example of a sex influenced trait is **pattern baldness** in humans (sometimes called "male pattern baldness," though the condition isn't restricted to males). This gene has two alleles, "bald" and "non-bald." The behaviors of the products of these genes are highly influenced by the hormones in the individual, particularly by the hormone testosterone. In the presence of high levels of testosterone, the baldness allele has a very powerful influence. In the presence of low levels of testosterone, this allele is quite ineffectual. All humans have testosterone, but males have much higher levels of this hormone than females do. The result is that in males, the baldness allele behaves like a dominant allele, while in females it behaves like a recessive allele. As in all cases, dominance only matters in the heterozygote, so this means that heterozygous males will experience hair loss and heterozygous females will not. Even homozygous females may experience no more than a thinning of their hair, but many develop bald spots or have receding hairlines.

An interesting note about this gene is that it is often incorrectly identified as X-linked because of an illusion that males inherit it from their mothers. Males can inherit baldness from either parent, but if a son gets it from his father, both father and son will be bald, and nobody really notices, as we expect sons to look reasonably like their fathers. But if a son loses his hair and his father **doesn't**, that's noteworthy, and the conclusion people have drawn (correctly) is that Junior inherited baldness from his mother. But recall that with X-linkage sons **always** inherit traits from their mothers and **never** from their fathers. In the case of baldness, a son can inherit from either parent. It's just that we notice it more in the case of inheritance from the mother. This is a kind of casual "sampling error," in which we subconsciously only "count" the surprising cases and conveniently forget the more ordinary ones.

Another instance of a sex influenced trait is in singing voice. The genetic influences that determine whether a person will have a high singing voice or a low one are autosomal, but the effects of the alleles are opposite in the two genders. The same allelic combination which produces a high soprano in a woman causes a male to be a low bass. And the combination that producers a high tenor in males produces a low contralto in females.

Barr Body and Dosage Compensation

The presence of two X chromosomes in normal human females and only one X in normal human males is unique compared with the equal numbers of autosomes present in the cells of both sexes. On theoretical grounds alone, it is possible to speculate that this disparity should create a “genetic dosage” difference between males and females, with attendant problems, for all X-linked genes. There is the potential for females to produce twice as much of each product of all X-linked genes.

A genetic mechanism of dosage compensation that balances the dose of X chromosome gene expression in females and males.

Murray L. Barr and Ewart G. Bertram’s experiments with fe-male cats, as well as Keith Moore and Barr’s subsequent study in humans, demonstrate a genetic mechanism in mammals that compensates for X chromosome dosage disparities. Barr and Bertram observed a darkly staining body in interphase nerve cells of female cats that was absent in similar cells of males.

Barr Body is about 1mm in diameter, lies against the nuclear envelope of interphase cells. It stains positively in the Feulgen reaction, a cytochemical test for DNA.Current experimental evidence demonstrates that this body, called a sex chromatin body, or simply a Barr body, is an inactivated X chromosome. Susumu Ohno was the first to suggest that the Barr body arises from one of the two X chromosomes. This hypothesis is attractive because it provides a possible mechanism for dosage compensa-tion. If one of the two X chromosomes is inactive in the cells of females, the dosage of genetic information that can be expressed in males and females will be equivalent.

The number of Barr bodies follows an N-1 rule, where Nis the total number of X chromosomes present. Although this apparent inactivation of all but one X chromosome increases our understanding of dosage compensation, it further complicates our perception of other matters. For example, because one of the two X chromosomes is inactivated in normal human females, why then is the Turner 45,X individual not entirely normal?

Why aren’t females with the triplo-X and tetra-X karyotypes (47,XXX and 48,XXXX) completely unaffected by the additional X chromosomes? Furthermore, in Klinefelter syndrome (47,XXY), X chromosome inactivation effectively renders the person 46,XY. Why aren’t these males unaffected by the extra X chromosome in their nuclei?

One possible explanation is that chromosome inactivation does not normally occur in the very early stages of development of those cells destined to form gonadal tissues. Another possible explanation is that not all of each X chromosome forming a Barr body is inactivated. Recent studies have indeed demonstrated that as many as 15 percent of the human X-chromosomal genes actually es-cape inactivation. Clearly, then, not every gene on the X re-quires inactivation. In either case, excessive expression of cer-tain X-linked genes might still occur at critical times during development despite apparent inactivation.

Lyon’s Hypothesis

In 1961, Mary Lyon and Liane Russell independently proposed a hypothesis that the in-activation of X chromosomes occurs randomly in somatic cells at a point early in embryonic development, most likely sometime during the blastocyst stage of develop-ment. Once inactivation has occurred, all descendant cells have the same X chromosome inactivated as their initial progenitor cell.

This explanation, called the Lyon hypothesis, was initially based on observations of female mice heterozygous for X-linked coat color genes. The pig-mentation of these heterozygous females was mottled, with large patches expressing the color allele on one X and other patches expressing the allele on the other X. This is the phenotypic pattern that would be expected if different X chromosomes were inactive in adjacent patches of cells. Similar mosaic patterns occur in the black and yellow-orange patches of female tortoise shell and calico cats. Such X-linked coat color patterns do not occur in male cats because all their cells contain the single maternal X chromo-some and are therefore hemizygous for only one X-linked coat color allele.

The most direct evidence in support of the Lyon hy-pothesis comes from studies of gene expression in clones of human fibroblast cells. Individual cells are isolated following biopsy and cultured in vitro. A culture of cells de-rived from a single cell is called a clone. The synthesis of the enzyme glucose-6-phosphate dehydrogenase (G6PD) is controlled by X linked gene.

Ronald Davidson and colleagues performed an experiment involving 14 clones from a single heterozygous female. Seven showed only one form of the enzyme, and 7 showed only the other form. Most important was the find-ing that none of the 14 clones showed both forms of the enzyme. Studies of G6PDmutants thus provide strong sup-port for the random permanent inactivation of either the maternal or paternal X chromosome.

The inactivation of an X chromosome into a Barr body is sometimes referred to as lyonization. One extension of the hypothesis is that mammalian females are mosaics for all heterozygous X-linked alleles—some areas of the body express only the maternally derived alleles, and others express only the paternally derived alleles. An especially interesting example involves red-green color blindness, an X-linked recessive disorder. In humans, hemizygous males are fully color-blind in all retinal cells. However, heterozygous females display mosaic retinas, with patches of defective color perception and surrounding areas with normal color perception.

The Mechanism of Inactivation

The least understood aspect of the Lyon hypothesis is the mechanism of X chromosome inactivation. Somehow, either DNA, the attached histone proteins, or both DNA and histone proteins, are chemically modified, silencing most genes that are part of that chromosome. Once silenced, a memory is created that keeps the same homolog inactivated following chromosome replications and cell divisions. Such a process, whereby expression of genes on one homolog, but not the other, is affected, is referred to as **imprinting.**

A region of the mammalian X chromosome is the major control unit. This region, located on the proximal end of the p arm in humans, is called the X inactivation center (Xic), and its genetic expression occurs only on the X chromosome that is inactivated. The Xicis about 1 Mb (10 e6 base pairs) in length and is known to contain several putative regulatory units and four genes.

One of these, X-inactive specific transcript (XIST), is now known to be a critical gene for X-inactivation. RNA that is transcribed from the XIST gene is quite large and does not encode a protein, and thus is not translated. The RNA products of Xist spread over and coat the X chromosome bearing the gene that produced them. Two other noncoding genes at the Xiclocus, Tsix(an antisense partner of Xist) and Xite,are also believed to play important roles in X-inactivation.

A second observation is that transcription of Xist initially occurs at low levels on all X chromosomes. As the in-activation process begins, however, transcription continues, and is enhanced, only on the X chromosome that becomes inactivated. In 1996, a research group led by Neil Brockdorff and Graeme Penny provided convincing evidence that transcription of Xist is the critical event in chromosome inactivation.

It has also been suggested that maternal and paternal X chromosomes must first pair briefly and align at their Xic loci as a mechanism for counting the number of X chromosomes prior to X-inactivation. This has been demonstrated by Lee *et al* by adding copies of genetically engineered non-X chromosomes containing multiple copies of Tsix or Xite. (These are referred to as transgenes because they are artificially introduced into the organism.) This experimental procedure effectively blocked X–X pairing and prevented X chromosome inactivation. Re-cent studies by Lee and colleagues have provided evidence that the inactivated X must associate with regions at the periphery of the nucleus to maintain a state of silenced gene expression. Indeed, in a majority of human female somatic cells the inactivated X, present as a Barr body, is observed attached to the nuclear envelope.

Sex Determination in Drosophila

Although both mammals and fruit flies produce XX females and XY males, their chromosomes achieve these ends using very different means. The sex-determining mechanisms in mammals and in insects such as *Drosophila* are very different. In mammals, the Y chromosome plays a pivotal role in determining the male sex. Thus, XO mammals are females, with ovaries, a uterus, and oviducts (but usually very few, if any, ova). In *Drosophila,* sex determination is achieved by a balance of female determinants on the X chromosome and male determinants on the autosomes. Normally, flies have either one or two X chromosomes and two sets of autosomes. If there is but one X chromosome in a diploid cell (1X:2A), the fly is male. If there are two X chromosomes in a diploid cell (2X:2A), the fly is female (Bridges 1921, 1925). Thus, XO *Drosophila* are sterile males. In flies, the Y chromosome is not involved in determining sex. Rather, it contains genes active in forming sperm in adults

X chromosomes	Autosome sets	(A)X:A ratio	Sex
3	2	1.50	Metafemale
4	3	1.33	Metafemale
4	4	1.00	Normal female
3	3	1.00	Normal female
2	2	1.00	Normal female
2	3	0.66	Intersex
1	2	0.50	Normal male
1	3	0.33	Metamale

In *Drosophila,* and in insects in general, one can observe **gynandromorphs**—animals in which certain regions of the body are male and other regions are female. This can happen when an X chromosome is lost from one embryonic nucleus. The cells descended from that cell, instead of being XX (female), are XO (male). Because there are no sex hormones in insects to modulate such events, each cell makes its own sexual "decision." The XO cells display male characteristics, whereas the XX cells display female traits. This situation provides a beautiful example of the association between insect X chromosomes and sex.

Any theory of *Drosophila* sex determination must explain how the X-to-autosome (X:A) ratio is read and how this information is transmitted to the genes controlling the male or female phenotypes. Although we do not yet know the intimate mechanisms by which the X:A ratio is made known to the cells, research in the past two decades has revolutionized our view of *Drosophila* sex determination. Much of this research has focused on the identification and analysis of the genes that are necessary for sexual differentiation and the placement of those genes in a developmental sequence. Several genes with roles in sex determination have been found. Loss-of-function mutations in most of these genes—*Sex-lethal* (*Sxl*), *transformer* (*tra*), and *transformer-2* (*tra2*)—transform XX individuals into males. Such mutations have no effect on sex determination in XY males. Homozygosity of the *intersex* (*ix*) gene causes XX flies to develop an intersex phenotype having portions of male and female tissue in the same organ. The *doublesex* (*dsx*) gene is important for the sexual differentiation of both sexes. If *dsx* is absent, both XX and XY flies turn into intersexes. The positioning of these genes in a developmental pathway is based on (1) the interpretation of genetic crosses resulting in flies bearing two or more of these mutations and (2) the determination of what happens when there is a complete absence of the products of one of these genes.