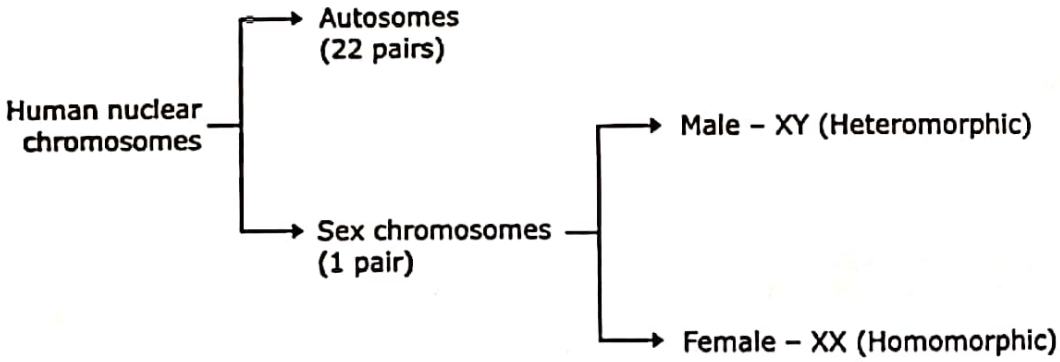
1.6 Sex chromosomes and sex determination

1.6.1 Sex chromosome

Most animals 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). Most of the chromosomes in a genome are autosomes. The sex chromosomes are fewer in number and majority of genes on the sex chromosomes are also not directly involved in sex determination.

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. There are two types of sex chromosomes in human– X and Y. In females, there is a pair of X-chromosomes. In males, there is a non-identical pair, consisting of one X and one Y. Hence, human females are **homomorphic** and males are **heteromorphic**. The Y-chromosome is considerably shorter than the X. The X and Y-chromosomes harbor different numbers of genes. The Human Genome Project has identified 397 possible genes on the human Y-chromosome, but fewer than 100 of them seem to be functional. By comparison, it has identified more than 1000 genes on the human X-chromosome.



During meiosis in females, the two X-chromosomes pair and segregate like autosomes so that each female gamete receives one X-chromosome. Hence, the female is said to be the **homogametic sex.** During meiosis in males, the X and Y-chromosomes pair and segregate so that half of the male gametes receive X and the other half receive Y. Therefore, the male is said to be the **heterogametic sex.**

The human Y-chromosome can be divided structurally into three regions:

1. Male-specific region of the Y-chromosome,
2. Pseudoautosomal regions (PAR1 and PAR2), and
3. Heterochromatin region.

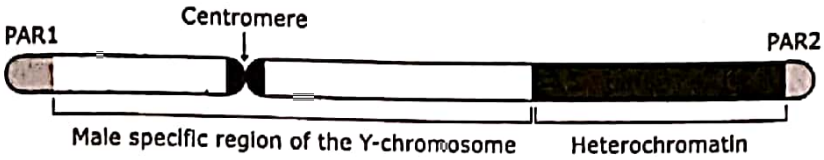


Figure 1.29 Schematic diagram of human Y-chromosome indicating the protein-coding genes within the male-specific region of the Y-chromosome, pseudoautosomal regions (PAR1 and PAR2) and heterochromatin region.

PARs contain 20 protein-coding genes (16 genes in PAR1 and 4 genes in PAR2). PARs are present in both X and Y-chromosomes. The pairing of the X and Y-chromosomes is made possible by a *major pseudoautosomal region* (PAR1) of 2.6 Mb located at the tips of the short arms of both chromosomes and a *minor pseudoautosomal region* (PAR2) of 320 kb located at the tips of the long arms of both chromosomes. Genes in the PAR1 segment have some interesting properties: they are not subject to X-inactivation and because of the crossing over, alleles at these loci do not show the normal X-linked or Y-linked patterns of inheritance, but segregate like autosomal alleles. The male-specific region of the Y-chromosome contains 23 protein-coding genes and numerous pseudogenes.

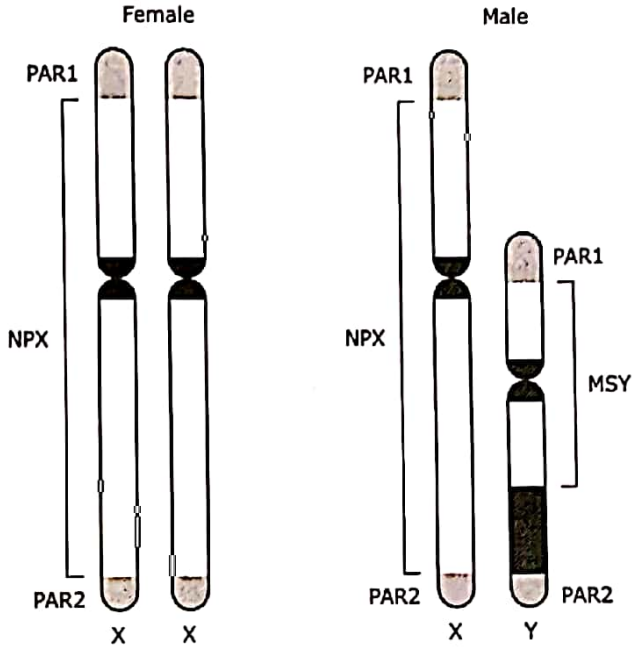


Figure 1.30 At each end of the human X and Y-chromosomes are the PARs, which recombine during meiosis and therefore contain the same genes. The non-pseudoautosomal portion of the X (NPX) and male-specific region of the Y (MSY) do not recombine with each other. Differences between X and Y arise because of differences in NPX and MSY genes.

1.6.2 Sex determination in animals

Whether an animal will become a male, a female, or a hermaphrodite is determined very early in development. *Hermaphrodites* are individuals that contain both male and female sex organs. Hermaphroditism is rare among animals. Some animals such as gastropods and earthworms are *simultaneous hermaphrodites* (e.g. simultaneously contain both male and female sexual organs) whereas many fishes are *sequential hermaphrodites* (born males and change into females or begin life as females and then change to males). Sex-determining mechanisms in animals are diverse. These mechanisms may be genotypic and environmental.

Genotypic sex determination

In genotypic sex determination, an individual's sex is established by its genotype (e.g. mammals, birds, amphibians, most insects, some reptiles and fish). In many animals, presence or absence of a particular chromosome or number of chromosomes determines the male and female sex. Basically, four types of chromosomal sex-determining mechanisms exist in animals: the XY, ZW, XO and haplodiploid system.

In the **XY system**, the females are *homogametic* with a pair of X-chromosomes (XX) and males are heterogametic with one X and Y-chromosomes (XY). Almost all mammals, many flies and some fishes, males are heterogametic.

In the **ZW system**, as in birds, snakes, butterflies, and some fishes; males are homogametic (ZZ), and females are heterogametic (ZW).

In the **XO system**, as in grasshopper; males have only one X-chromosome (XO) and females have two X-chromosomes (XX).

In **haplodiploid systems**, as in honey bees, male progeny normally develops from unfertilized eggs, which are haploid and have just one set of chromosomes. The fertilized honey bee eggs, which are diploid and have two sets of chromosomes, differentiate into queens and worker bees. Thus, in honey bees, sex is determined by the fertilization or non-fertilization of eggs, rather than the presence or absence of sex chromosomes.

Different systems of sex determination

1. XY system (Example - Human)	XX (female)	XY (male)
2. XO system (Example - Grasshopper)	XX (female)	XO (male)
3. ZW system (Example - Birds)	ZW (female)	ZZ (male)
4. Haplodiploid system (Example - Honey bees)	Diploid (female)	Haploid (male, drones)
	Worker bee (imperfect female)	
	Queen (perfect female)	

Problem

Sex determination in grasshopper is by the XO method. The somatic cells of a grasshopper are analyzed and found to contain 23 chromosomes.

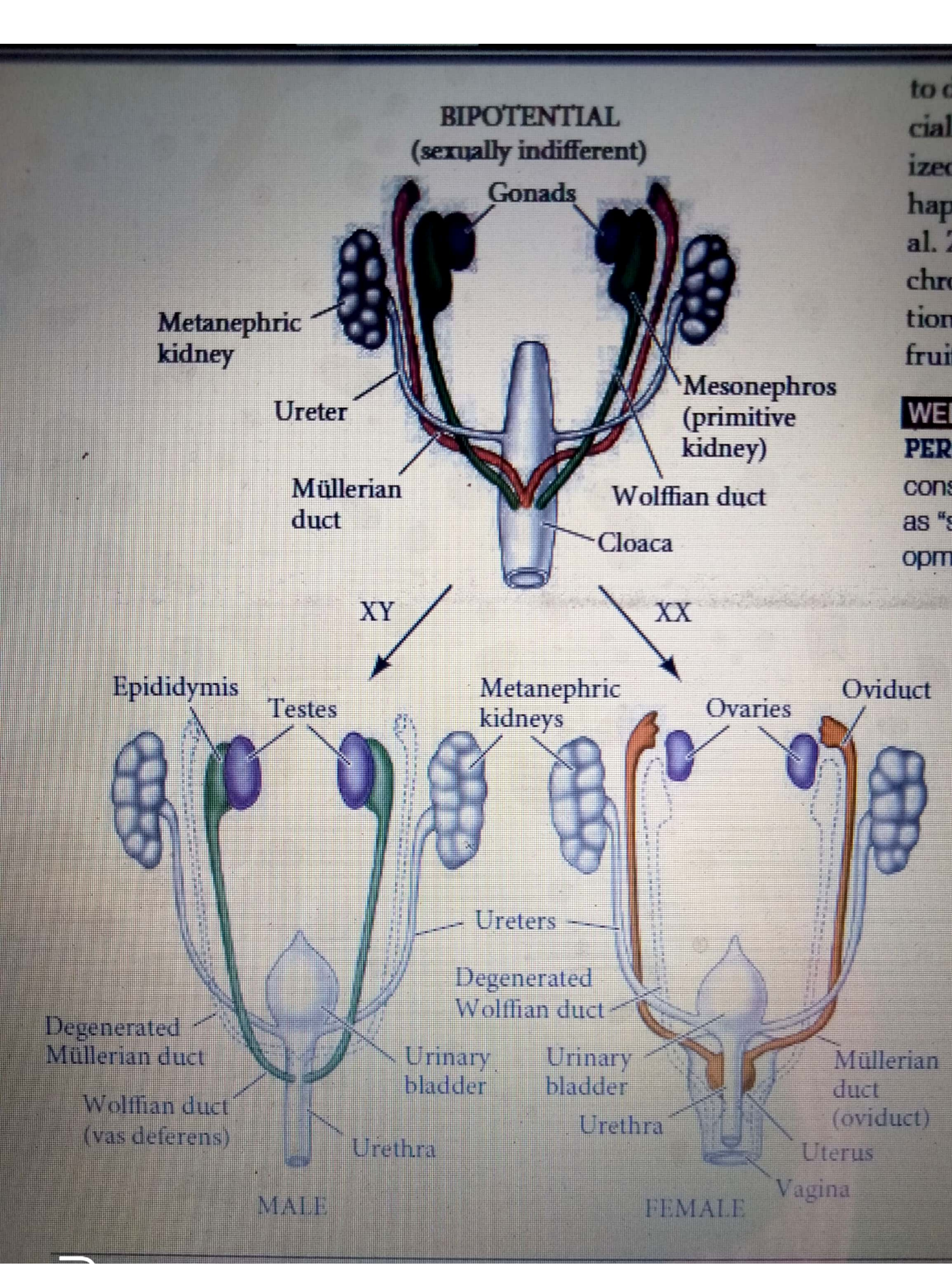
1. What sex is this individual?
2. Determine the frequency with which different types of gametes (number of autosomes and sex chromosomes) can be formed in this individual.
3. What is the diploid number of the opposite sex?

Solution

1. Male
2. 1/2(11A + 1X) : 1/2(11A)
3. 24

Environmental sex determination

Sex is also determined by environmental factors, such as temperature, pH, social interactions and seasonality. In many species, sex is determined by the temperature at which the egg is incubated during a temperature sensitive period and cannot be predicted by zygotic genotype. This peculiar mechanism is termed **temperature-dependent sex determination.** The temperature dependent sex determination has been shown to exist in all crocodiles and the majority of turtles along with a few species of lizards. In these reptiles, the temperature of the eggs during a certain period of development is the deciding factor in determining sex, and small changes in temperature can cause dramatic changes in the sex ratio. Often, eggs incubated at low temperatures produce one sex, whereas eggs incubated at higher temperatures produce the other. There are several hypotheses concerning the physiological control of sex determination by temperature, but there is little conclusive evidence in support of molecular basis involved. In some species, sex steroid hormones serve as an important factor for male and female sex determination. It appears that the enzyme **aromatase** (which can convert testosterone into estrogen) is important in temperature dependent sex determination in turtle. The activity of aromatase or its synthesis is temperature sensitive. Aromatase activity is higher at female- than at male-producing temperatures.



Sex determination in mammals

The sex of eutherian (or placental) mammal is determined by its sex chromosomes. Primary sex determination is dictated by whether an organism has an XX or an XY karyotype. Females have two X-chromosomes in all of their somatic cells whereas males have one X and one Y. Individuals with a Y-chromosome develop as males no matter how many X-chromosomes they have, whereas individuals without a Y-chromosome develop as females. Thus, primary sex determination is based on the presence of the Y-chromosome. Primary sex determination is the determination of the gonads—the egg-forming ovaries or sperm-forming testes. In contrast, secondary sex determination is the determination of the male or female phenotype by the hormones produced by the gonads.

Males develop functional testes. Both the ovaries and testes diverge from a common precursor, the **bipotential gonad** (sometimes called the **indifferent gonad**). Testes are induced from the bipotential gonad by the activity of the protein encoded by the **Sex-determining Region Y** (*Sry*), located on the Y-chromosome. This protein is called **sex-determining region Y protein** (also known as **testis-determining factor**). When Sry protein is not present, as in XX individuals, or non-functional in XY individuals, the bipotential gonads generally do not follow the testicular pathway and instead develop into ovaries. Considerable evidence suggests that the *Sry* gene is necessary to initiate testes development. Sry protein is a transcription factor with a DNA-binding high-mobility group box domain. It binds to the enhancer of the autosomal gene *Sox9* (SRY-related HMG BOX gene 9) and elevates expression of this key gene in the testis-determining pathway. If **Sox9** is expressed ectopically in the developing gonads of an XX mouse embryo, the embryo develops as a male, even if it lacks the *Sry* gene, suggesting that Sry normally acts by inducing the expression of *Sox9 gene*. The Sox9 protein acts as a transcription factor. It is expressed in males in all vertebrates, unlike Sry, which is found only in mammals. The Sox9 protein activates **Fgf9** (fibroblast growth factor 9) synthesis, which stimulates testis development. Sox9 and Sry also act to block the ovary-forming pathway, possibly by blocking **β-catenin.**

Sry gene is expressed only in a subset of the mesodermal cells of the developing gonad and it causes these cells to differentiate into **Sertoli cells**, which are the main type of supporting cells found in the testes. The autosomal gene *Sox9* is also known to be essential for Sertoli cell differentiation. The Sertoli cells produce an **anti-Mullerian hormone** (also called *Müllerian-inhibiting factor*), which suppresses the development of the female reproductive tract by causing the mullerian duct to regress. This duct otherwise gives rise to the oviduct, uterus, and upper part of the vagina. Meanwhile, the other group of mesoderm cells (those that did not form the Sertoli epithelium) differentiate into a mesenchymal cell type, the testosterone-secreting **Leydig cells**. The male sex hormone **testosterone** is responsible for inducing all male secondary sexual characters.

In the absence of normal Sry expression, the cortex of the undifferentiated gonad develops into an ovary. The supporting cells become **follicle cells** instead of Sertoli cells. Other somatic cells become **theca cells** instead of Leydig cells and, secrete the female sex hormone **estrogen** instead of *testosterone*. Estrogen enables the development of the Müllerian duct into the uterus, oviducts, cervix and upper portion of the vagina. This normal process of female development is sometimes referred to as the 'default' pathway.

Genic balance theory of sex determination in *Drosophila*

Fruit flies also have XX females and XY males. However, the mechanism of sex determination in *Drosophila* differs from that in mammals. In mammals, the Y-chromosome plays a pivotal role in determining the male sex. In *Drosophila*, the Y-chromosome is not involved in determining sex. Rather, in *Drosophila*, genes present on the Y-chromosome involved in sperm formation in adults, but not in sex determination. Calvin Bridges suggested in 1921 that sex in *Drosophila* is determined by the balance (ratio) of autosomal alleles that favour maleness and alleles on the X-chromosomes that favour femaleness. He found that a ratio of X-chromosomes to autosomal sets determines the sex of *Drosophila*. A normal diploid male contains 2 sets of autosomes and XY-chromosomes. Similarly, a normal diploid female has 2 sets of autosomes and two X-chromosomes.

Table 1.3 Sex determination by genic balance in *Drosophila*

Number of X-chromosome	*Number of Autosomal sets (A)*	*Total number of chromosomes*	*X/A ratio*	*Sex*
3	2	9	1.5	Meta female
2	2	8	1.00	Female
1	1	4	1	Female
2	3	11	0.67	Intersex
1	2	7	0.50	Male
1	3	10	0.33	Meta male

Bridges results show that in *Drosophila* factors that cause a fly to develop into a male are not localized on the sex chromosome, but are instead found on the autosomes. X-chromosomes contain genes for some female-determining factors. A sex switch gene directs the female development. This sex switch gene termed sex-lethal (*Sxl*) is located on the X-chromosome. In the *on* state, it diverts female development and in the *off* state maleness. Other genes located on the X-chromosome and the autosomes regulate this sex switch gene. Activation of the *Sxl* gene relies on a ratio of X-chromosomes to sets of autosomes. The presence of the Y-chromosome in *Drosophila,* although it is essential for male fertility, has nothing to do with the determination of sex.

Drosophila gynandromorph

A *gynandromorph* is an organism that contains both male and female characteristics. A gynandromorph can have bilateral asymmetry, half female and half male, or they can be mosaic. A classic example is the *Drosophila* gynandromorph. Such conditions arise as a result of non-disjunction or chromosomal lagging during mitosis in the zygote or in nuclei in the early embryo. If one of the X-chromosome is lost in one of the dividing somatic cells, it results in an XX cell line and an XO cell line. If this chromosomal lagging occurs early in the development, a *Drosophila* that is part male (XO) and part female (XX) develops. A gynandromorph can have bilateral asymmetry, in which chromosomal lagging has occurred at the one-cell stage i.e. during the first mitotic division, causing the fly to be half male and half female. *Gynandromorphs differ from the intersexes.* **Intersexes** are genetically similar throughout their bodies and usually sterile, but a gynandromorph consists of two genetically different tissues.

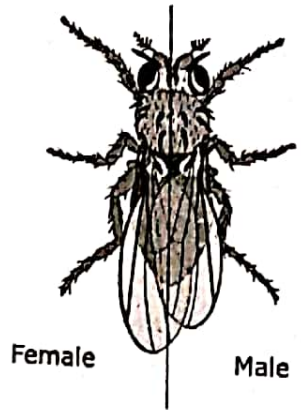


Figure 1.31 Gynandromorphs in *Drosophila.*

Chromosomal Sex Determination in *Drosophila*

Although both mammals and fruit flies produce XX females and XY males, the ways in which their chromosomes achieve these ends are very different. In mammals, the Y chromosome plays a pivotal role in determining the male sex. In *Drosophila*, the Y chromosome is not involved in determining sex. Rather, in flies, the Y chromosome

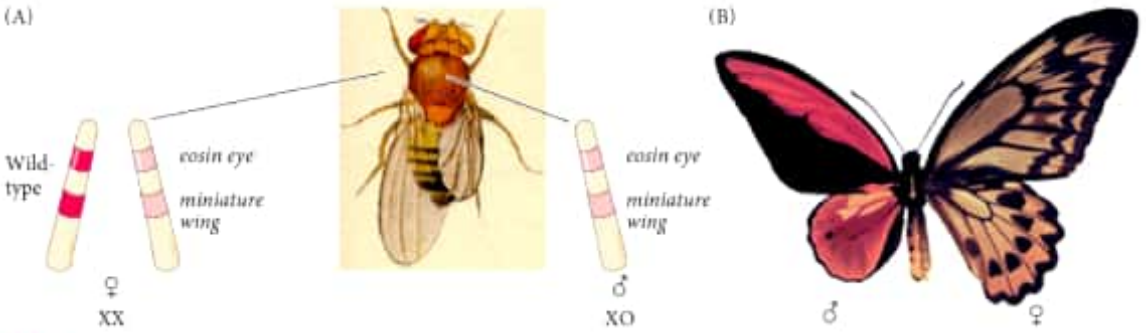


FIGURE 6.13 Gynandromorph insects. (A) *D. melanogaster* in which the left side is female (XX) and the right side is male (XO). The male side has lost an X chromosome bearing the wild-type alleles of eye color and wing shape, thereby allowing expression of the recessive alleles *eosin eye* and *miniature wing* on the remaining X chromosome. (B) Birdwing butterfly *Ornithoptera croesus*. The smaller male half is red, black, and yellow, while the female half is larger and brown. (A, drawing by Edith Wallace from Morgan and Bridges 1919; B, Montreal Insectarium, photograph by the author.)

seems to be a collection of genes that are active in forming sperm in adults, but not in sex determination.

A fruit fly's sex is determined predominantly by the number of X chromosomes in each cell. If there is only one X chromosome in a diploid cell, the fly is male. If there are two X chromosomes in a diploid cell, the fly is female. Should a fly have two X chromosomes and three sets of autosomes, it is a **mosaic**, where some of the cells are male and some of the cells are female. Thus, while XO mammals are sterile females (no Y chromosome, thus no *Sry* gene), XO *Drosophila* are sterile males (one X chromosome per diploid set).

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 (**FIGURE 6.13**). Gynandromorph fruit flies result when an X chromosome is lost from one embryonic nucleus. The cells descended from that cell, instead of being XX (female), are XO (male). The XO cells display male characteristics, whereas the XX cells display female traits, suggesting that, in *Drosophila*, each cell makes its own sexual "decision." Indeed, in their classic discussion of gynandromorphs, Morgan and Bridges (1919) concluded, "Male and female parts and their sex-linked characters are strictly self-determining, each developing according to its own aspiration," and each sexual decision is "not interfered with by the aspirations of its neighbors, nor is it overruled by the action of the gonads." Although there are organs that are exceptions to this rule (notably the external genitalia), it remains a good general principle of *Drosophila* sexual development.

The Sex-lethal gene

Although it had long been thought that a fruit fly's sex was determined by the X-to-autosome (X:A) ratio (Bridges 1925), this assessment was based largely on flies with aberrant numbers of chromosomes. Recent molecular analyses suggest that X chromosome number alone is the primary sex determinant in normal diploid insects (Erickson and Quintero 2007). The X chromosome contains genes encoding transcription factors that activate the critical gene in *Drosophila* sex determination, the X-linked locus ***Sex-lethal*** (***Sxl***). The Sex-lethal protein is a splicing factor that initiates a cascade of RNA processing events that will eventually lead to male-specific and female-specific transcription factors (**FIGURE 6.14**). These transcription factors (the Doublesex proteins) then differentially activate the genes involved to produce either the male phenotype (testes, sex combs, pigmentation) or the female phenotype (ovaries, yolk proteins, pigmentation).

ACTIVATING *SEX-LETHAL* The number of X chromosomes appears to have only a single function: activating (or not activating) the early expression of *Sex-lethal*.[6] *Sxl* encodes an RNA splicing factor that will regulate gonad development and will also

[6] This gene's gory name is derived from the fact that mutations of this gene can result in aberrant dosage compensation of X-linked genes (see Web Topic 6.6). As a result, there is inadequate transcription of those genes encoded on the X chromosome, and the embryo dies.

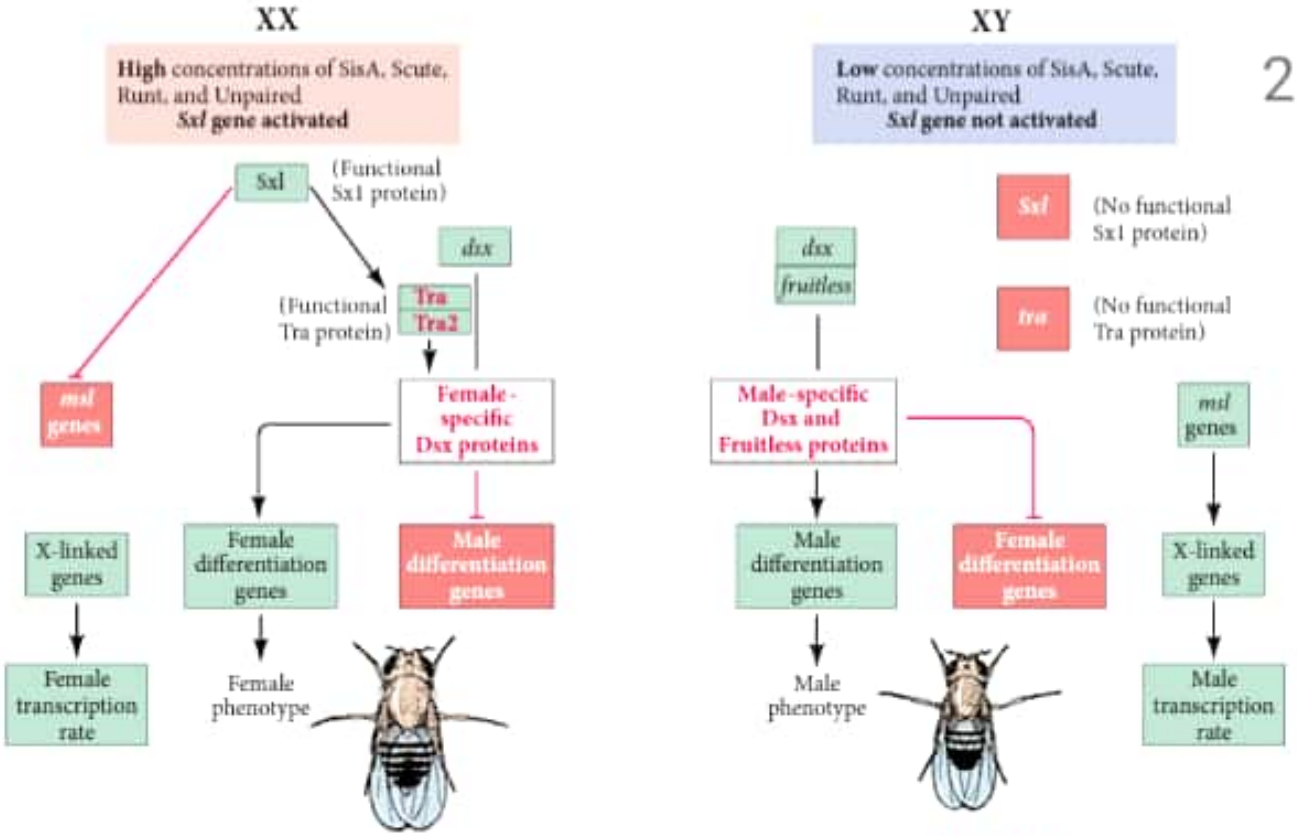


FIGURE 6.14 Proposed regulatory cascade for *Drosophila* somatic sex determination. Transcription factors from the X chromosomes activate the *Sxl* gene in females (XX) but not in males (XY). The Sex-lethal protein performs three main functions. First, it activates its own transcription, ensuring further Sxl production. Second, it represses the translation of *msl2* mRNA, a factor that facilitates transcription from the X chromosome. This equalizes the amount of transcription from the two X chromosomes in females with that of the single X chromosome in males. Third, Sxl enables the splicing of the *transformer-1* (*tra1*) pre-mRNA into functional proteins. The Tra proteins process *doublesex* (*dsx*) pre-mRNA in a female-specific manner that provides most of the female body with its sexual fate. They also process the *fruitless* pre-mRNA in a female-specific manner, giving the fly female-specific behavior. In the absence of Sxl (and thus the Tra proteins), *dsx* and *fruitless* pre-mRNAs are processed in the male-specific manner. (The *fruitless* gene is discussed in Web Topic 6.7.) (After Baker et al. 1987.)

regulate the amount of gene expression from the X chromosome. The gene has two promoters. The early promoter is active only in XX cells; the later promoter is active in both XX and XY cells. The X chromosome appears to encode four protein factors that activate the early promoter of *Sxl*. Three of these proteins are transcription factors—SisA, Scute, and Runt—that bind to the early promoter to activate transcription. The fourth protein, Unpaired, is a secreted factor that reinforces the other three proteins through the JAK-STAT pathway (Sefton et al. 2000; Avila and Erickson 2007). If these factors accumulate so they are present in amounts above a certain threshold, the *Sxl* gene is activated through its early promoter (Erickson and Quintero 2007; Gonzáles et al. 2008; Mulvey et al. 2014). The result is the transcription of *Sxl* early in XX embryos, during the syncytial blastoderm stage.

The *Sxl* pre-RNA transcribed from the *early* promoter of XX embryos lacks exon 3, which contains a stop codon. Thus, Sxl protein that is made early is spliced in a manner such that exon 3 is absent, so early XX embryos have complete and functional Sxl protein (**FIGURE 6.15**). In XY embryos, the early promoter of *Sxl* is not active and no functional Sxl protein is present. However, later in development, as cellularization is taking place, the *late* promoter becomes active and the *Sxl* gene is transcribed in both males and females. In XX cells, Sxl protein from the early promoter can bind to its own pre-mRNA and splice it in a "female" direction. In this case, Sxl binds to and blocks the splicing complex on exon 3 (Johnson et al. 2010; Salz 2011). As a result, exon 3 is skipped and is not included in the *Sxl* mRNA. Thus, early production ensures that functional full-length (354-amino acid) Sxl protein is made if the cells are XX (Bell et al. 1991; Keyes et al. 1992). In XY cells, however, the early promoter is not active (because the X-encoded transcription factors haven't reached the threshold to activate the promoter) and there is no early Sxl protein. Therefore, the *Sxl* pre-mRNA of XY cells is spliced in a manner that *includes* exon 3 and its termination codon. Protein synthesis ends at the third exon (after amino acid 48), and the Sxl is nonfunctional.

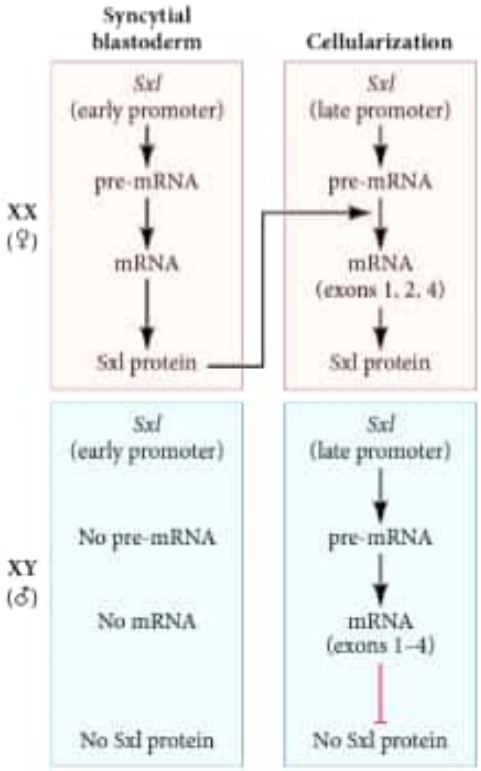


FIGURE 6.15 Differential RNA splicing and sex-specific expression of *Sex-lethal*. In the syncytial blastoderm of XX flies, transcription factors from the two X chromosomes are sufficient to activate the early promoter of the *Sxl* gene. This "early" transcript is spliced into an mRNA lacking exon 3 and makes a functional Sxl protein. The early promoter of XY flies is not activated, and males lack functional Sxl. By the cellularizing blastoderm stage, the late promoter of *Sxl* is active in both XX and XY flies. In XX flies, Sxl already present in the embryo prevents the splicing of exon 3 into mRNA and functional Sxl protein is made. Sxl then binds to its own promoter to keep it active; it also functions to splice downstream pre-mRNAs. In XY embryos, no Sxl is present and exon 3 is spliced into the mRNA. Because of the termination codon in exon 3, males do not make functional Sxl. (After Salz 2011.)

WEB TOPIC 6.6 DOSAGE COMPENSATION If the cells of female flies, nematodes, and mammals have twice the number of X chromosomes as male cells, how are the genes on the X chromosome regulated? The three groups offer three different solutions to the problem.

TARGETS OF SEX-LETHAL The protein made by the female-specific *Sxl* transcript contains regions that are important for binding to RNA. There appear to be three major RNA targets to which the female-specific *Sxl* transcript binds. One of these is the pre-mRNA of *Sxl* itself. Another target is the *msl2* gene that controls dosage compensation (see below). Indeed, if the *Sxl* gene is nonfunctional in a cell with two X chromosomes, the dosage compensation system will not work, and the result is cell death (hence the gene's name). The third target is the pre-mRNA of *transformer* (*tra*)—the next gene in the cascade (**FIGURE 6.16**; Nagoshi et al. 1988; Bell et al. 1991).

The pre-mRNA of *transformer* (so named because loss-of-function mutations turn females into males) is spliced into a functional mRNA by Sxl protein. The *tra* pre-mRNA is made in both male and female cells; however, in the presence of Sxl, the *tra* transcript is alternatively spliced to create a female-specific mRNA, as well as a nonspecific mRNA that is found in both females and males. Like the male *Sxl* message, the nonspecific *tra* mRNA message contains an early termination codon that renders the protein nonfunctional (Boggs et al. 1987). In *tra*, the second exon of the nonspecific mRNA contains the termination codon and is not utilized in the female-specific message (see Figures 6.14 and 6.16).

How is it that females and males make different mRNAs? The female-specific Sxl protein activates a 3′ splice site that causes *tra* pre-mRNA to be processed in a way that splices out the second exon. To do this, Sxl protein blocks the binding of splicing factor U2AF to the nonspecific splice site of the *tra* message by specifically binding to the polypyrimidine tract adjacent to it (Handa et al. 1999). This causes U2AF to bind to the lower-affinity (female-specific) 3′ splice site and generate a female-specific mRNA (Valcárcel et al. 1993). The female-specific Tra protein works in concert with the product of the *transformer-2* (*tra2*) gene to help generate the female phenotype by splicing the *doublesex* gene in a female-specific manner.

Doublesex: The switch gene for sex determination

The *Drosophila* **doublesex** (**dsx**) gene is active in both males and females, but its primary transcript is processed in a sex-specific manner (Baker et al. 1987). This alternative RNA processing is the result of the action of the *tra* and *tra2* gene products on the *dsx* gene (see Figures 6.14 and 6.16). If the Tra2 and female-specific Tra proteins are both present, the *dsx* transcript is processed in a female-specific manner (Ryner and Baker 1991). The female splicing pattern produces a female-specific protein that activates female-specific genes (such as those of the yolk proteins) and inhibits male development. If no functional Tra is produced, a male-specific *dsx* transcript is made; this transcript encodes a transcription factor that inhibits female traits and promotes male traits. In the embryonic gonad, Dsx regulates all known aspects of sexually dimorphic gonad cell fate.

In XX flies, the female Doublesex protein (Dsx^F) combines with the product of the *intersex* gene (*ix*) to make a transcription factor complex that is responsible for promoting female-specific traits. This "Doublesex complex" activates the *Wingless* (*Wg*) gene, whose Wnt-family product promotes growth of the female portions of the genital disc. It also represses the *Fgf* genes responsible for making male accessory organs, activates the genes responsible for making yolk proteins, promotes the growth of the sperm storage duct, and modifies *bricabrac* (*bab*) gene expression to give the female-specific pigmentation profile. In contrast, the male Doublesex protein (Dsx^M) acts directly as a transcription

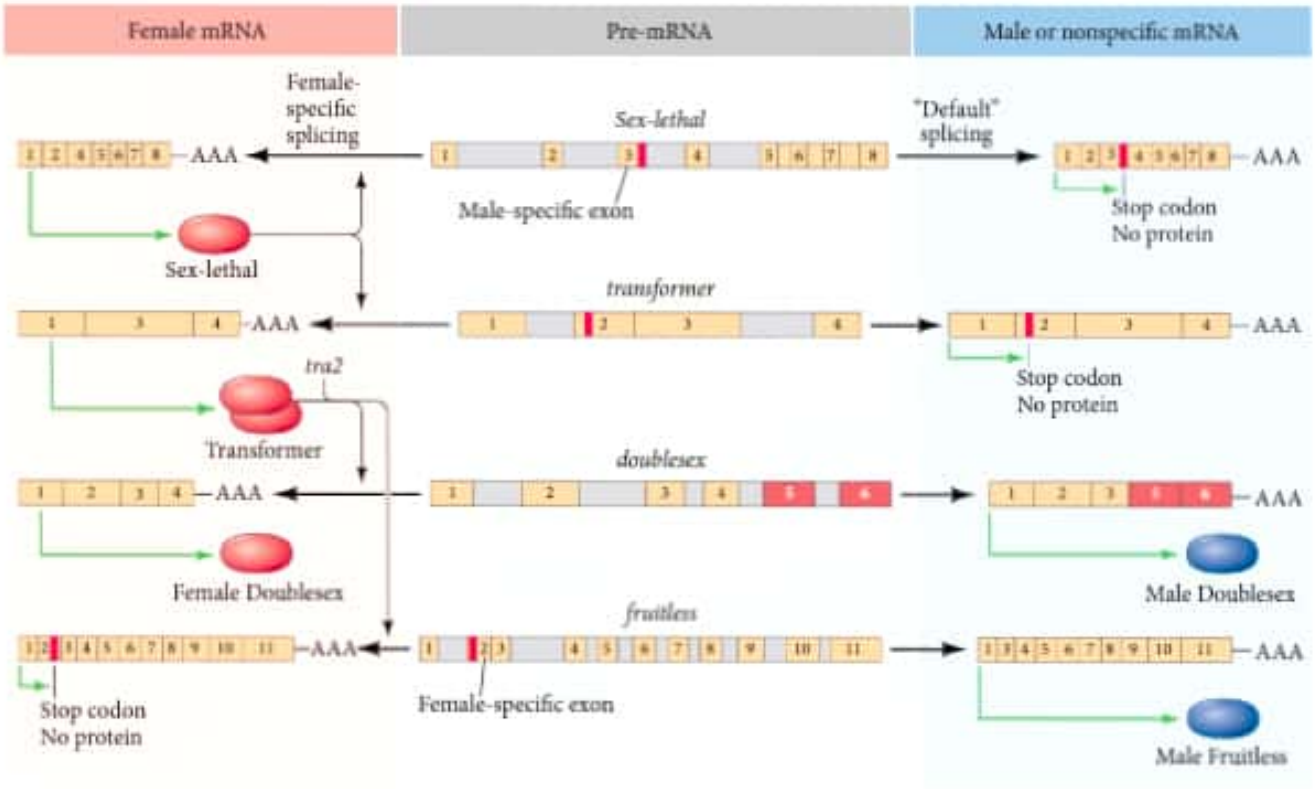


FIGURE 6.16 Sex-specific RNA splicing in four major *Drosophila* sex-determining genes. The pre-mRNAs (shown in the center of diagram) are identical in both male and female nuclei. In each case, the female-specific transcript is shown at the left, while the default transcript (whether male or nonspecific) is shown to the right. Exons are numbered, and the positions of termination codons are marked. *Sex-lethal*, *transformer*, and *doublesex* are all part of the genetic cascade of primary sex determination. The transcription pattern of *fruitless* determines the secondary characteristic of courtship behavior. (After Baker 1989; Baker et al. 2001.)

factor and directs the expression of male-specific traits. It causes the male region of the genital disc to grow at the expense of the female disc regions. It activates the BMP homologue *Decapentaplegic* (*Dpp*), as well as stimulating *Fgf* genes to produce the male genital disc and accessory structures. Dsx^M also converts certain cuticular structures into claspers and modifies the *bricahrac* gene to produce the male pigmentation pattern (Ahmad and Baker 2002; Christiansen et al. 2002).

According to this model, the result of the sex determination cascade summarized in Figure 6.14 comes down to the type of mRNA processed from the *doublesex* transcript. If there are two X chromosomes, the transcription factors activating the early promoter of *Sxl* reach a critical concentration, and *Sxl* makes a splicing factor that causes the *transformer* gene transcript to be spliced in a female-specific manner. This female-specific protein interacts with the *tra2* splicing factor, causing *dsx* pre-mRNA to be spliced in a female-specific manner. If the *dsx* transcript is not acted on in this way, it is processed in a "default" manner to make the male-specific message. Interestingly, the *doublesex* gene of flies is very similar to the *Dmrt1* gene of vertebrates, and the two types of sex determination may have some common denominators.

WEB TOPIC 6.7 **BRAIN SEX IN *DROSOPHILA*** In addition to the "doublesex" mechanism for creating sexual phenotypes in *Drosophila*, a separate "brain sex" pathway characterized by the *fruitless* gene provides individuals with the appropriate set of courtship and aggression behaviors.