4 SEX CHROMOSOMES AND SEX DETERMINATION

4.1 Sex chromosomes and Sex Determination

Sex- chromosomes. If present, sex chromosomes may not have the same size, shape, or genetic potential. In humans, females have 2 so-called **X chromosomes** and males have one X chromosome and one **Y chromosome**. The human X and Y not strictly homologous. Y is much smaller and lacks most of loci contained on the X. They do behave as homologs during meiosis, however.

Soon after the rediscovery of Mendel's work, experiments with *Drosophila* produced results in which the phenotypic proportions differed between males and females. These results were explained by postulating that the genes were located on the X chromosome of *Drosophila*, which is present in two copies in females, but only one copy in males.

Mammals, birds, some insects, and a few plants have this kind of sex chromosome system. One sex has a pair of homologous chromosomes, whereas the other sex has one chromosome that resembles the homologous pair, and one different chromosome.

Mammals and *Drosophila*	females have two X chromosomes:	*XX*
	males have one X chromosome and one Y:	*XY*

These are the "**sex chromosomes**", all other chromosomes are called "**autosomes**".
The sex with two different chromosomes is the **heterogametic sex.** The other is the **homogametic sex.**

For the X chromosome then, female mammals and *Drosophila* have two copies of each gene on the X, but males have only one. Females can be homozygous or heterozygous, but males are **hemizygous**.

Birds and Lepidoptera (Moths and Butterflies) have the opposite pattern: Males are homogametic (*ZZ*) and females are heterogametic (*ZW*).

4.2 The Mammalian X Chromosome

The X chromosome carries hundreds of genes but few, if any, of these have anything to do directly with sex. However, the inheritance of these genes follows special rules. These arise because:

* males have only a single X chromosome
* almost all the genes on the X have no counterpart on the Y; thus
* any gene on the X, even if recessive in females, will be expressed in males.

Genes inherited in this fashion are described as sex-linked or, more precisely, X-linked.

X-Linkage: An Example
Hemophilia A is a blood clotting disorder caused by a mutant gene encoding the clotting factor VIII. This gene is located on the X chromosome. With only a single X chromosome, males who inherit the defective gene (always from their mother) will be unable to produce factor VIII

and suffer from difficult-to-control episodes of bleeding. In heterozygous females, the un-mutated copy of the gene will provide all the factor VIII they need. Heterozygous females are called "carriers" because although they show no symptoms, they pass the gene on to approximately half their sons, who develop the disease, and half their daughters, who also become carriers.

	X	**Y**
X	XX	XY
X^h	X^hX	X^hY

Women rarely suffer from hemophilia A because to do so they would have to inherit a defective gene from their father as well as their mother. Until recently, few hemophiliacs ever became fathers.

4.3 The Mammalian Y Chromosome

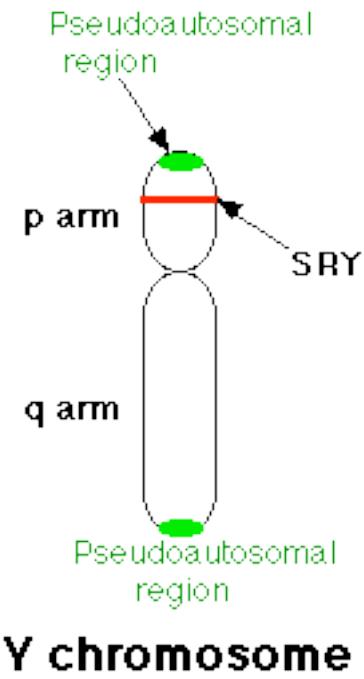
In making sperm by meiosis, the X and Y chromosomes must separate in Meiosis I just as homologous autosomes do (if you don't remember what happens in Meiosis I vs. Meiosis II, this would be a good time to review. You will need to know this in order to understand much of the remainder of this course!) This occurs without a problem because, like homologous autosomes, the X and Y chromosome synapse during **prophase** of meiosis I. There is a small region of homology shared by the X and Y chromosome and synapsis occurs at that region.

Crossing over between the X and the Y occurs in two regions of pairing, called the **pseudoautosomal regions**. These are located at opposite ends of the chromosome.

The Pseudoautosomal Regions:

The pseudoautosomal regions get their name because any genes located within them (so far only 9 have been found) are inherited just like any autosomal genes. Males have two copies of these genes: one in the pseudoautosomal region of their Y, the other in the corresponding portion of their X chromosome. So males can inherit an allele originally present on the X chromosome of their father and females can inherit an allele originally present on the Y chromosome of their father.

This diagram shows the structure of the human Y chromosome.



Y chromosome

Genes outside the pseudoautosomal regions:

Although 95% of the Y chromosome lies between the pseudoautosomal regions, fewer than 80 genes have been found here. Some of these encode proteins used by all cells (and both sexes). The others encode proteins that appear to function only in the testes. A key player in this latter group is SRY.

4.4 SRY and Mammalian Sex Determination

It is often stated that sex determination in humans is based on the presence or absence of the Y chromosome. However, the situation is more complex. Sex determination in humans and other mammals is actually due to a **single gene** that is normally located on the Y chromosome. Near one of the pseudoautosomal regions, but not in it, is the **SRY** ("sex-determining region"). The SRY produces a gene product, **TDF (testis determining factor),** that triggers undifferentiated gonadal tissue in embryos to form testes. SRY has been found in all mammals investigated.

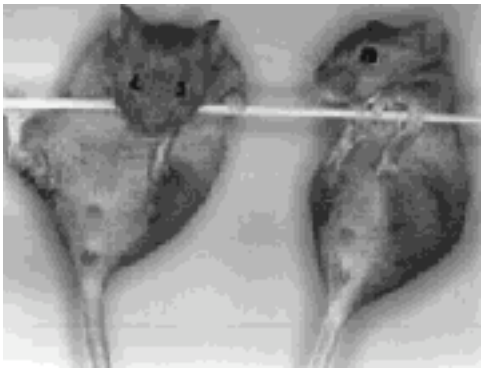
The gene functions early in the developmental program that ultimately causes tissue that is developing into ovaries to 'switch' their development, so that they develop as testes. Individuals without this gene develop as females. Sometimes, the SRY gene becomes associated with a chromosome other than the Y. In these cases, an individual can have the chromosome complement XY, and be a perfectly normal female (or be XX and be a normal male).

SRY is a gene located on the short (p) arm just outside the pseudoautosomal region. It is the master switch that triggers the events that converts the embryo from it's 'defaul' developmental pattern as a female into a developmental sequence that results in a male. If this gene is absent or inactivated, a mammal develops into a female, even if the Y chromosome itself is present. Therefore it is not the Y chromosome that determines maleness, or the presence of two X chromosomes that determines femaleness, it is the presences or absence of the protein coded for by the SRY gene that determines gender in mammals.

What is the evidence?

On very rare occasions aneuploid humans are born with such karyotypes as XXY, XXXY, and even XXXXY. Despite their extra X chromosomes, all these cases are male.

This image (courtesy of Robin Lovell-Badge from Nature 351:117, 1991) shows two mice with an XX karyotype (and thus they should be female). However, as you may be able to see, they have a male phenotype. This is because they are transgenic for SRY. Fertilized XX eggs were injected with DNA carrying the SRY gene.



Although these mice have testes, male sex hormones, and normal mating behavior, they are sterile. Other genes on the Y are required for normal fertility.

Still another rarity that demonstrates the case: women with an XY karyotype who, despite their Y chromosome, are female because of a destructive mutation in SRY.

(A test based on a molecular probe for SRY was used to ensure that potential competitors for the women's Olympic events in Atlanta had no SRY gene.)

4.5 Dosage Compensation and X inactivation

Human females (and females of all other mammal species) inherit two copies of every gene on the X chromosome, whereas males inherit only one (with 18 exceptions: the 9 pseudoautosomal genes and the 9 "housekeeping" genes found on the Y). But for the hundreds of other genes on the X, are males at a disadvantage in the amount of gene product their cells produce? The answer is no, because females have only a single active X chromosome in each cell.

During interphase, chromosomes are too tenuous to be stained and seen by light microscopy. However, a dense, stainable structure, called a Barr body (after its discoverer) is seen in the interphase nuclei of female mammals. The Barr body is one of the X chromosomes. Its compact appearance reflects its inactivity. So, the cells of females have only one functioning copy of each X-linked gene - the same as males. The inactivation of one of the two X chromosomes in female equalizes the **gene dosage** of X-linked genes—this is known as **dosage compensation.**

The Lyon Hypothesis. A female mammal inherits one X chromosome from her mother and one from her father, which one gets inactivated? In 1961 Mary Lyon and Lianne Russell proposed that early in development, one or the other of the X chromosomes becomes inactivated in each cell of the developing embryo. Which one is inactivated is random. All the cells that arise by cell division from a particular early embryonic cells will have the same X inactivated. This leads to adult females being **mosaics** for X-linked genes. This hypothesis has become widely accepted: X-inactivation does appear to occur early in embryonic development. In a given cell, which of a female's two X chromosomes becomes inactivated and converted into a Barr body does seem to be a matter of chance (except in marsupials like the kangaroo, where it is always the father's X chromosome that is inactivated). And female mammals are genetic mosaics for genes on the X chromosome (see below).

4.5.1 Mechanism of X-inactivation

Inactivation of an X chromosome requires a gene on that chromosome called XIST.

XIST encodes a large molecule of RNA (of a type different from those used in protein synthesis such as mRNA). XIST RNA accumulates along the X chromosome containing the active XIST gene and proceeds to inactivate all (or almost all) of the other hundreds of genes on that chromosome. XIST RNA does not travel over to any other X chromosome in the nucleus. Barr bodies are inactive X chromosomes "painted" with XIST RNA.

During the first steps of embryonic development of the female, the XIST locus on each of her two X chromosomes is expressed but the XIST RNA is quickly broken down. Then something happens to tip the balance in favor of one or the other of the X chromosomes.

Transcription continues on one of the X chromosomes, leading to an accumulation of XIST RNA and converting that chromosome into an inactive Barr body. Transcription of XIST ceases on the other X chromosome allowing all of its hundreds of other genes to be expressed. The shut-down of the XIST locus on the active X chromosome is done by methylating XIST regulatory sequences. DNA methylation usually results in gene repression so methylation permanently blocks XIST expression and permits the continued expression of all the other X-linked genes.

X-inactivation in the female embryo appears to be entirely random. There is no predicting whether it will be the maternal X or the paternal X that is inactivated in a given cell. But that is not the case for her extraembryonic membranes (that go on to form the amnion, placenta, and umbilical cord). In all the cells of the extraembryonic membranes, it is father's X chromosome that is inactivated.

Some genes on the X chromosome escape inactivation:
What about those 18 genes that are found on the Y as well as the X? There should be no need for females to inactivate one copy of these to keep in balance with the situation in males. And, as it turns out, these genes escape inactivation in females. Just how they manage this has yet to be discovered.

Other kinds of organisms do not accomplish dosage compensation in the same way that mammals do. For example: There is no X inactivation in *Drosophila*. Male X-linked genes are transcribed at **twice the rate** of genes on the X of a female. Mutations at several **autosomal genes** in males decrease the rate of transcription, and are lethal.

4.6 Support for the Lyon Hypothesis

The Lyon hypothesis is supported because mosaicism can sometimes be directly observed in females that are heterozygotes for X-linked genes. For example: 1) females heterozygotes for the gene causing red-green color blindness have mosaic of normal and defective retinal cells; and 2) **tortoiseshell and calico cats** are females that are heterozygotes for black/orange hair color (Bb).

Why does Turner syndrome occur at all, since only one X chromosome is normally active? There are two active X chromosomes during ovarian development, and certain genes appear to need to be active for normal ovarian function. The inactive X chromosome is reactivated in oogonia when meiosis begins during fetal life. There are also extra copies of all the genes that are found on both the X and Y, since these are not inactivated.

4.7 Human disorders associated with sex chromosome abnormalities:

47,XXY Klinefelter syndrome male tall stature testes do not mature sterile lowered IQ is common 1/700 male births	**45,X Turner Syndrome (XO)** female short stature rudimentary ovaries sterile IQ typically normal 1/3000 female births
47,XYY Double-Y syndrome male above average height, otherwise phenotypically normal. At one time, it was claimed that XYY males are prone to violent or antisocial behavior, based on elevated incidence of 47,XYY among incarcerated men. Now thought to be due to higher incidence of moderate mental retardation than for XY males.	**47,XXX Trisomy-X syndrome** many phenotypically normal the frequency of lowered IQ is higher than among XX females.

4.8 Variation in sex determining mechanisms

4.8.1 Sex Determination in *Drosophila*

Although *Drosophila* have X and Y chromosomes, sex determination is not dependent on the Y chromosome. The **ratio of X chromosomes to autosomes determines sex** in these insects. The Y chromosome does not cause maleness, but contains genes necessary for male fertility.

XXY	X0
normal female	sterile male

Normal complement of autosomes and sex chromosomes:

females	**males**
X X 2X:2A	X Y 1X:2A
II II	II II
III III	III III
IV IV	IV IV

	Sex Chromosomes			
	X X	X Y	X X Y	X O
Drosophila	Female	Male	Female	Male
Mammals	Female	Male	Male	Female

Sexual Phenotypes of *D. melanogaster*

# of X chromosomes	# of sets of autosomes	Gentoype	X/A ratio	Sexual Phenotype	Sexual Phenotype
2	2	XX; 2A	1	fertile	female
1	2	XY: 2A	0.5	feritle	male
1	2	XO; 2A	0.5	sterile	male
3	2	XXX; 2A	1.5	sterile	metafemale
1	3	X; 3A	0.33	sterile	metamale
2	3	XX; 3A	0.67	characteristics of both sexex	intersex

4.8.2 Sex Determination in other organisms

Reptiles and many other groups of plants and animals display a great deal of diversity in their sex-determining mechanisms. For example:

Most snakes have a ZZ/ZW sex-determining system in which females are the heterogametic sex.

In most lizards, both XX/XY and ZZ/ZW systems are found.

In crocodiles, most turtles, and some lizards, sex is not genetically determined at all, but is determined by the incubation temperature during a critical period of embryo development. This is known as temperature-dependent sex determination (TSD).

TSD itself comes in at least three different forms:

a) low temperatures yield females and high temperatures produce males
b) low temperatures produce males and high temperatures produce females
c) low and high temperatures produce females, while intermediate temperatures produce male

4.9 Genomic Imprinting

This term refers to the differential expression of genetic traits depending on whether the trait has been inherited from a mother or a father. Another way to think of genomic imprinting is as "parent of origin differences" in the expression of inherited traits.

For most genes there is no difference in expression whether the allele has been inherited from the mother or from the father, but some genes are influenced by their parental origin. They have a 'imprint' of their gametic origin.

The occurrence of imprinting in mammals has only recently been recognized, and was deduced from a number of different lines of research, including classical genetic studies, studies on X-inactivation, and the development of diploid parthenogenetic (gynogenetic, and androgenetic) embryos.

Most regions of the genome are converted to gene products equally from the maternally and paternally derived members of a chromosome pair. For a few specific regions, however, this is not true, and the genetic information in a portion of certain chromosomes is inactivated when inherited from one sex parent but not when inherited from the other.

In these so-called imprinted regions, only one copy of the genes is transcribed, the other remaining genetically silent (at least in somatic cells). It is not completely evident why genes are imprinted. The most prominent assumption is that this process is necessary for development and may somehow regulate growth in the embryo and neonate. Evidence for this suggestion came from experiments with mouse androgenotes (embryos with two paternal genomes) and gynogenotes (embryos with two maternal genomes), which were produced by nuclear transplantation. These zygotes were formed, but neither type was able to undergo further development. From this situation, it is possible to suggest that the maternal and paternal effects are complementary (Browder et al., 1991). Each genome contains different viable and necessary properties (Barlow, 1995). Further evidence that genomic imprinting plays a major role in growth and development comes from research by Li et al. (1993).