Garriga lecture notes 3/4/09
Read pp 65-75

Sex determination

Sex is determined in many ways.
Certain reptiles become male or female depending on the temperature that the eggs are incubated. If the eggs of alligators are incubated below 30ºC, they become females; if incubated above 34ºC, they become females. Temperature can have the opposite effect on certain turtles, with higher temperatures favoring females and lower temperatures favoring males. In other turtle species, intermediate temperatures favor female development and higher and lower temperatures favor male development. Sex in some turtle species is determined by sex chromosomes. Sex can be determined by interactions with other members of the species. Clownfish, for example, are hermaphrodites, with the dominant male becoming a female after the female of the group dies. The point of these examples is not to make you memorize a bunch of facts about animal sex determination, but to reveal the diverse mechanisms that can be involved. These examples only scratch the surface of the possibilities and illustrate how fast sex evolves.

We focused in how sex chromosomes determine sex in two organisms: fruit flies and mammals. Most of what we know about sex determination in fruit flies comes from work on *Drosophila melanogaster* and what we know about mammals comes from studies in humans and mice. Sex chromosomes are chromosomes that differ in the two sexes. One sex is homogametic or has a pair of the same sex chromosomes, and the other sex is heterogametic or has two different chromosomes. When males are the homogametic sex, the sex chromosomes are labeled W and Z, and males are ZZ and females ZW. Examples of species with homogametic males and heterogametic females are butterflies and birds.

When females are the homogametic sex, then the sex chromosomes are named X and Y. Both Drosophila and mammalian females are XX and males XY. This does not mean that the genes on the X chromosomes of flies and mammals are the same. In fact, simply by looking at the sex of aneuploid individuals, we can see that sex in these two species is determined in fundamentally different ways (Figure 1). In mammals, if the animal has a Y chromosome, it is a male; if it lacks a Y, it is a female. The number of X chromosomes makes no difference. In Drosophila, by contrast, the presence or absence of the Y chromosome does not correlate with sex. X0 individuals are male; XXY individuals are female. Early in the 19th century, Calvin Bridges showed that the ratio of X chromosomes to sets of autosomes determines sex in Drosophila. When the ratio is 0.5, the fly is a male; when the ratio is 1.0, the fly is female. When Bridges manipulated this ratio to be between 0.5 and 1.0, the animals were intersexual having both male and female traits.

	mammals	Drosophila
XX	female	female
XY	male	male
XO	female	male
XXY	male	female
XYY	male	male

Figure 1.

What is on Y?
The mammalian Y chromosome has very few genes. Half of the genes are in a region called the pseudoautosomal region. This region gets its name because as with autosomes, it shared homology with the other sex chromosome, the Y. During meiosis I, homologs need to pair to ensure proper segregation. In females, there is no problem because there are two X chromosomes, but in males, the X and Y must pair so that they can segregate away from each other in meiosis I. The homology between the peudoautosomal region ensures that X and Y chromosomes pair in male meiosis. Because this region is homologous between X and Y, crossing over occurs. About half of the genes on the Y are in this region and are shared with X. The remaining genes are unique to Y. They encode proteins involved in male fertility and SRY, the protein that determines male sexual development.

It became clear that a gene next to the pseudoautosomal region determines sex when it was discovered that rare XY women and rare XX men existed. (We will discuss later XY women that lack the androgen receptor, but the gonads of these women develop into testes.) In these cases the XY females (they had ovaries) were lacking a region next to the pseudoautosomal region and the XX males had this region attached to the X chromosome. Some of these abnormal chromosomes were generated by unequal crossing over between the X and Y in the male parent. Identifying the DNA sequences absent on the abnormal X chromosome in XX males and the extra sequences on the abnormal Y chromosome led to the identification of the *SRY* (Sex-determining Region on Y) gene, which is both necessary and sufficient for male development. There are rare XY females that have a mutation that inactivates the *SRY* gene. This observation showed that SRY is necessary for male development. Experiments in mice confirmed this and showed that *SRY* is also sufficient: inserting the *SRY* gene on an autosome caused transgenic XX mice to develop as males.

How does SRY determine maleness?
The *SRY* gene encodes a transcription factor. By binding to DNA sequences near specific genes, the SRY protein sets into motion a series of developmental events that causes the immature gonad to become a testes. During embryonic development, we all had gonads that had the potential to become either testes or ovaries. SRY caused them to develop as testes; the absence of SRY resulted in ovaries. The testes synthesize two chemicals that specify male sex organ development: testosterone and anti-Mullerian Hormone (AMH). We also start of with two duct systems, the Mullerian and Wolffian duct systems, which form the internal sex organs of the female and male, respectively. In XY males, AMH causes the Mullerian duct system to degenerate. Testosterone causes the Wolffian duct system to develop into the internal structures of the male. Testosterone is converted into the more powerful androgen dihydroxytestosterone (DHT) by the enzyme 5-alpha reductase. DHT then promotes the development of the external male structures, for example, the penis and scrotum.

While AMH and testosterone are both hormones, they are different biochemically. Testosterone is a steroid. It does not dissolve in aqueous environments, but is lipid

soluble and can cross the plasma membrane of the cell, which is a lipid bilayer. Once inside the cell, it binds to a receptor that is in the cytoplasm. The testosterone/receptor complex then enters the nucleus, binds to DNA sequences near specific genes and regulates the transcription of the genes. In other words, the testosterone/steroid complex is a transcription factor. This type of receptor is called a nuclear hormone receptor. AMH, by contrast, is a peptide hormone. Because it is a peptide, AMH is soluble in water and cannot cross the plasma membrane. Instead, peptide hormones like AMH bind to protein receptors that are imbedded in the plasma membrane. Binding to the extracellular portion of the receptor causes a change in the intracellular portion of the membrane. This change then leads to events that also regulate transcription of specific genes. You do not need to know the details of this intracellular signaling, but like many other membrane receptors, the AMH receptor is a kinase, which means is can add a phosphate group to other proteins. Phosphorylation changes the activity of the modified protein.

Because the ovaries do not produce much testosterone, the Mullerian duct system develops into the internal female structures. The Wolffian duct system degenerates in the absence of testosterone. In the absence of testosterone, external female structures like the labia and clitoris develop.

We will cover three genetic syndromes next time that cause XX individuals that take on male characteristics or XY individuals that adopt female traits.