



Genetic Mechanisms of Sex Determination

By: Laura Hake, Ph.D. (*Biology Department, Boston College*) & Clare O'Connor, Ph.D. (*Biology Department, Boston College*) © 2008 Nature Education

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In 335 B.C.E., Aristotle proposed that the heat of the male partner during intercourse determined sex. At least in the case of reptiles, Aristotle was on to something. What about in other animals?

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Whether an animal will become a male, a female, or a hermaphrodite is determined very early in **development**. Scientists have worked for hundreds of years to understand the sex-determination system. For instance, in 335 B.C.E., Aristotle proposed that the heat of the male partner during intercourse determined sex. If the male's heat could overwhelm the female's coldness, then a male child would form. In contrast, if the female's coldness was too strong (or the male's heat too weak), a female child would form. Environmental theories of **sex determination**, such as Aristotle's, were popular until about 1900, when **sex chromosomes** were discovered. As it turns out, Aristotle was on to something, at least in the case of some reptiles, in which the temperature of the nest determines the **sex** of the **embryo**. For most animals, however, sex is determined chromosomally.

Sex Chromosomes

Sex determination results in the development of individuals with characteristics that allow them to be identified as males, females, or in some cases, hermaphrodites. In certain **species**, like the solid nematode *C. elegans*, differences in sexual characteristics can be very small; in fact, in *C. elegans*, the only distinguishing sexual **characteristic** is the presence of a testis versus an ovotestis. In other species, the phenotypic differences between the sexes can be quite significant. Consider, for example, the remarkable plumage and display of a tom turkey versus the rather plain features of a female turkey. Female and male mammals are also readily distinguished by many differences in their internal and external phenotypes, behavior, and **metabolism**.

The first major breakthrough in understanding sex determination was the discovery of sex chromosomes in the early 1900s. From meticulous analyses of male and female insect chromosomes, scientists discovered that, although most chromosomes were present in equal numbers in both males and females, there were one or two additional chromosomes that were unequally represented in the two sexes. Analyses of additional species over the years has revealed that chromosomal differences are primarily responsible for sex determination in most animals.

Chromosomal Mechanisms of Sex Determination in Insects

Insects are the most diverse class of organisms on the planet, so it is not too surprising that they show considerable diversity in their mechanisms of sex determination (Saccone *et al.*, 2002). However, like most other animals, the majority of insects have dimorphic sex chromosomes that can be distinguished cytologically.

Animals with two different sex chromosomes are of **heterogametic sex**, and they are thus able to produce two types of **gametes**. Conversely, members of the **homogametic sex** can only produce one type of gamete. In humans (as well as many other animals), males generally have one X and one **Y chromosome**, while females have two X chromosomes. This system is reversed in butterflies and moths (order Lepidoptera): females are the heterogametic sex, while males are homogametic. The sex chromosomes in Lepidoptera are designated W and Z. W chromosome is usually associated with the development of female characteristics. When the W chromosome is absent, ZZ develops into males and ZO develop into females. Having a W chromosome to develop as a female isn't even a necessity for some species. A moth known as *Talaeporia tubulosa* uses the ambient temperature to control sex determination in the absence of W **chromosome**. When temperatures are warm, the Z chromosome is found on the inner **spindle** and more female eggs are produced, whereas in colder conditions, the Z chromosome moves to the outer pole, resulting in greater production of males (Traut *et al.*, 2007). This system corresponds to the adaptive advantage of favoring the production of female **offspring** when conditions are good (warm) and resources for their subsequent **reproduction** are more likely to be available.

Some grasshoppers also use a single-chromosome (XX/XO) sex determination system; here, males have only one sex chromosome, so they are considered to be XO. Thus, males are the heterogametic sex, because they produce two different kinds of gametes.

The system of chromosomal sex determination is even further reduced in certain genera of mosquitoes, in which the two sexes are chromosomally indistinguishable. Sex in this homogametic group is thought to be determined by a **dominant** male-determining factor.

Sex Determination in Drosophila

The sex chromosomes of the fruit fly *Drosophila melanogaster* have played a particularly important role in our understanding of heredity. Therefore, it may come as a surprise that fruit flies use a relatively rare mechanism to determine sex. In fact, in *Drosophila*, sex is primarily determined by the **X:A ratio**, or the ratio of the number of X chromosomes to the number of sets of autosomes (Cline & Meyer, 1996). The balance between female-determining factors encoded on the X chromosome and male-determining factors encoded on the autosomes determines which sex-specific pattern of **transcription** will be initiated. Thus, XX, XXY, and XYY flies are females, while XY and XO flies are males. Flies are unable to survive with more than two copies of an X chromosome because of the mechanism that they use for **dosage compensation**. (Dosage compensation refers to the processes by which animals equalize the amount of **gene** products generated from X-linked **genes** in males and females. Unlike in mammals, all of the *Drosophila* X chromosomes remain active, and flies adjust the levels of X-linked gene products by doubling expression from the X chromosome in males. An extra copy of the X chromosome, which contains close to one-third of fly genes, creates an aneuploid condition that greatly disrupts the **equilibrium** in cells.)

Drosophila sex determination also differs from mammalian sex determination in several other ways. First, sex determination begins immediately at fertilization, and there is no indifferent period. Furthermore, hormones are not responsible for sex-specific traits; instead, each cell in the embryo senses the X:A ratio, triggering either the female- or male-specific pattern of transcription. Microarray experiments indicate that the sex-specific differences in gene expression are quite extensive. In fact, roughly 30% of *Drosophila* genes were found to show sex-specific biases in expression (Parisi *et al.*, 2004).

Sex Determination in Mammals

In placental mammals, the presence of a Y chromosome determines sex. Normally, cells from females contain two X chromosomes, and cells from males contain an X and a Y chromosome. Occasionally, individuals are born with sex chromosome aneuploidies, and the sex of these individuals is always determined by the absence or presence of a Y chromosome. Thus, individuals with 47,XXY and 47,XYY karyotypes are males, while individuals with 45,X and 47,XXX karyotypes are females. Humans are able to tolerate supernumerary numbers of sex chromosomes because of X inactivation and the fact that the human Y chromosome is quite gene-poor.

Although the role of the Y chromosome in mammalian sex determination has been known since the early twentieth century, it was not until 1959 that scientists were able to identify the region of the Y chromosome that controlled this process (McLaren, 1991). Later, researcher David C. Page analyzed the chromosomes of sex-reversed XX men, rare individuals who look like men but have two X chromosomes instead of one X chromosome and one Y chromosome. Using DNA hybridization with probes corresponding to different regions of the Y chromosome, Page discovered that sex-reversed males carried genes from a 140-kilobase region on the short arm of the Y chromosome (Figure 1). Presumably, this region had been transferred to the X chromosome during a translocation (Page *et al.*, 1985). Subsequent experiments narrowed down this region (McLaren, 1991) and found that one gene, the sex-determining region of the Y, or SRY, was the master regulator of sex determination. The presence of just this region from the Y chromosome is thus sufficient to cause male development (Koopman *et al.*, 1991).

In human embryos, the SRY gene encodes a unique transcription factor that activates a testis-forming pathway at about week seven of development. Before this time, the embryonic gonad is "indifferent," meaning that it is capable of developing into either a testis or an ovary (Figure 2). Likewise, the early embryo has two systems of ducts, Wolffian and Müllerian ducts, which are capable of developing into the male and female reproductive tracts, respectively. Once the SRY gene product stimulates the indifferent gonad to develop into a testis, the testis begins producing two hormones, testosterone and anti-Müllerian hormone, or AMH. Testosterone and one of its derivatives, dihydrotestosterone, induce formation of other organs in the male reproductive system, while AMH causes the degeneration of the Müllerian duct. In females, who do not contain the SRY protein, the ovary-forming pathway is activated by a different set of proteins. The fully developed ovary then produces estrogen, which triggers development of the uterus, oviducts, and cervix from the Müllerian duct.

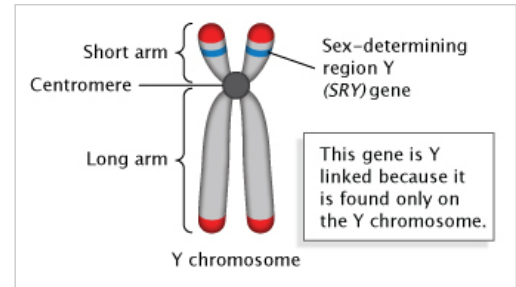


Figure 1: Location of the sex-determining region Y (SRY) gene on the Y-chromosome.

The SRY gene (blue band) on the male Y chromosome regulates sex determination in mammals.

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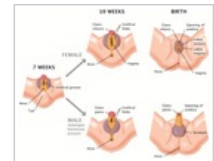


Figure 2

Figure Detail

Sex Determination in Birds: Z and W Chromosomes

In birds, sex is determined by chromosomes known as the Z and W, and females are the heterogametic sex. Early on, it was apparent that there were notable differences in the mechanisms used for sex determination in birds and mammals. Working with chickens, scientists were unable to find a counterpart of the SRY gene required for mammalian testis determination, so they searched for homologues of other genes that were required for testis formation in mammals. These investigations led to the discovery of the *DMRT1* gene on the chicken Z chromosome (Nanda *et al.*, 1999).

In mammals, the *DMRT1* gene product is a critical member of the testis-forming pathway initiated by *SRY*. Two copies of the *DMRT1* gene are necessary for testis development, even in the presence of *SRY*. In mammals, both sexes have two copies of *DMRT1*, because it is located on an autosome (specifically, chromosome 9). In chickens, by contrast, only males possess two copies of *DMRT1*, as it is located on the Z chromosome. Figure 3 shows the results of an *in situ* hybridization experiment in which a *DMRT1* probe has been hybridized to the chromosomes of a female chicken. Figure 3b shows the appearance of the chromosomes under a microscope, and Figure 3a shows that the *DMRT1* probe hybridizes to a single region on the female's Z chromosome. (These are metaphase chromosomes, so hybridization is detected on the two sister chromatids.) Figure 3c shows selected chromosomes in a partial karyotype. One can readily see that the Z chromosome is significantly larger than the W chromosome.

The actual trigger for activating the testis-forming pathway in chickens remains unknown. Birds also differ significantly from mammals in that two unique genes on the W chromosome, *FET1* and *ASW*, are necessary for female development. The function of *FET1* is unknown, but it is expressed in the gonads leading up to the time of sexual differentiation (Smith & Sinclair, 2004). Like mammals, chickens also have an indifferent gonad until around day four of development, after which an ovary or a testis starts to develop. Hormones then orchestrate the development of other sex-specific characteristics. In contrast with mammals, however, estrogen is required earlier in sex determination in chickens, and is, in fact, necessary for formation of the ovary. In fact, genetically male chickens can be converted to females if eggs are injected with estrogen at the sensitive stage of development.

The ZZ-ZW mechanism of sex determination is not restricted to birds. Within the vertebrates, a similar system of sex determination has been identified in reptiles, as well as in some fishes and amphibians.

Sex Determination and Environment

As previously mentioned in the discussion of *Talaeopora tubulosa*, environmental factors can sometimes play an important role in sex determination. Insects are not a special case—among the vertebrates, temperature also has a strong influence on sex determination in certain groups of reptiles. For example, in crocodilian reptiles and most turtles, sex is determined by egg incubation

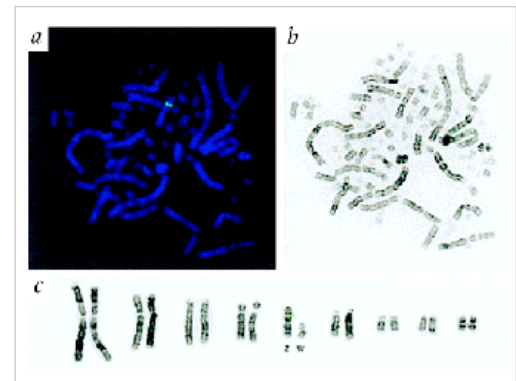


Figure 3: FISH mapping of DMRT1 on chicken Z chromosome.

a. Hybridization of DMRT1 cosmid to a female chicken metaphase spread. b. DAPI banding of the same metaphase spread, converted into G-like bands. c. G-banded karyotype of chicken macrochromosomes hybridized with DMRT1 (green spot on Z chromosome).

© 1999 Nature Publishing Group Nanda, I. *et al.* 300 million years of conserved synteny between chicken Z and human chromosome 9. *Nature Genetics* 21, 259 (1999). All rights reserved.



temperature. There are several variations on this theme. In the alligator snapping turtle, *Macrolemys temminckii*, incubation of eggs below 22°C or above 28°C gives rise to females, while incubation at intermediate temperatures produces predominantly males. American alligators show a similar biphasic dependence on temperature, but the curve is shifted to higher temperatures. In the European pond turtle, *Trachemys scripta*, incubation temperatures above 30°C produce all females, whereas incubation temperatures below 25°C produce all males. At 28.5°C, equal numbers of males and females are produced.

The temperature-dependent component of the sex-determination pathway has been studied in great detail in the European turtle, *Emys orbicularis*. In *E. orbicularis*, the critical temperature-dependent component appears to be synthesis of the **enzyme** aromatase, which converts androgens, such as testosterone, into estrogens. At higher temperatures, increased aromatase activity produces more estrogens, which biases the **sex ratio** toward more females.

As one compares the various mechanisms for sex determination among species, it is clear that **evolution** has produced numerous solutions for generating different sexes. **Sexual reproduction** has tremendous adaptive value to a species, because it introduces new genetic variability into a **population** in each new generation. Chromosomes play determinative roles in most species, but even so, environmental factors introduce additional wrinkles into the developmental process.

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