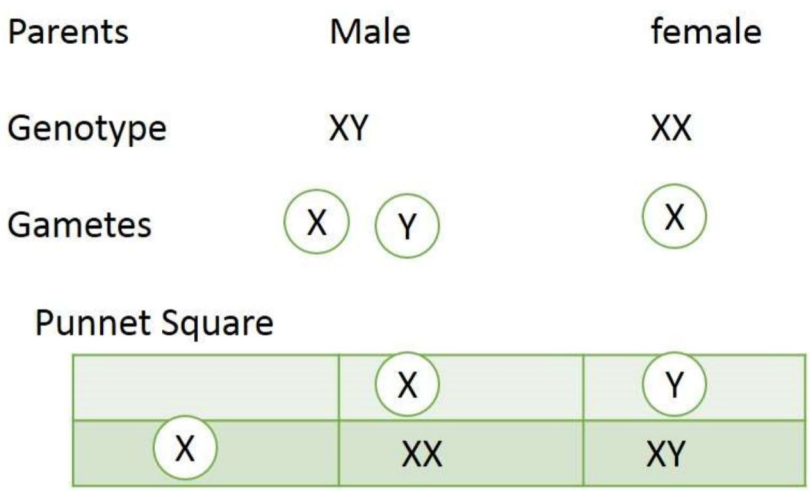
Sex Determination - III

Sex Determination in Human Beings

The XO genotype in human beings is a female (with Turner syndrome), hence, the Y chromosome is male determining. The fact that persons with Klinefelter syndrome (XXY, XXXY, XXXXY) are all male, and XXX, XXXX, and other multiple-X karyotypes are all female, supports this idea.



For a long time, researchers have sought a single gene, a **testis-determining factor (TDF)**, located on the Y chromosome that acts as a sex switch to initiate male development. Human embryologists had discovered that during the first month of embryonic development, the gonads that develop are neither testes nor ovaries, but instead are indeterminate. At about six or seven weeks of development, the indeterminate gonads become either ovaries or testes.

In the 1950s, Ernst Eichwald found that males had a protein on their cell surfaces not found in females; he discovered that female mice rejected skin grafts from genetically identical brothers, whereas the brothers accepted grafts from sisters. This implies that an antigen exists on the surface of male cells that is not found on female cells. This protein was called the *histocompatibility*

Y antigen (H-Y antigen). The gene for this protein was found on the Y chromosome, near the centromere. At first, scientists believed it to be the sex switch: if the gene were present, the gonads would begin development as testes. Further male development, as in male secondary sexual characteristics, came about through the testosterone the functional testes produced. If the gene were absent, the gonads would develop into ovaries. Recently, however, by studying "sexreversed" individuals, biologists refuted this theory.

Sex-reversed individuals are XX males or XY females. David Page, at the Whitehead Institute for Biomedical Research, found twenty XX males who had a small piece of the short arm of the Y chromosome attached to one of their X chromosomes. He found six XY females in whom the Y chromosome was missing the same small piece at the end of its short arm. This region, which did not contain the *HYA* gene, must carry the testis-determining factor. The first candidate gene from this region believed to code for the testis-determining factor was named the *ZFY* gene, for zinc finger on the Y chromosome. Zinc fingers are protein configurations known to interact with DNA. Thus, researchers believed that the *ZFY* gene, coding for the testis-determining factor, worked by directly interacting with DNA.

However, men who lack the *ZFY* gene have been found, suggesting that the testis-determining factor is very close to, but not, the *ZFY* gene.

From work in mice, it has been suggested that the *ZFY* gene controls the initiation of sperm cell development, but not maleness.

In 1991, Robin Lovell-Badge and Peter Goodfellow and their colleagues in England isolated a gene called Sex-determining region Y (*SRY*)—*Sry* in mice—adjacent to the *ZFY* gene. *Sry* has been positively identified as the

testis-determining factor because, when injected into normal (XX) female mice, it caused them to develop as males. Although these XX males are sterile, they appear as normal males in every other way. However, at present, the human *SRY* gene does not convert XX female mice into males. Like the *ZFY* gene product, Sry protein (the protein the *SRY* gene produces) also binds to DNA. The Sry protein appears to bind to at least two genes.

One, the p450 aromatase gene, has a protein product that converts the male hormone testosterone to the female hormone estradiol; the Sry protein inhibits production of p450 aromatase. The second gene the Sry protein affects is the gene for the Müllerian-inhibiting substance, which induces testicular development and the digression of female reproductive ducts; the Sry protein enhances this gene's activity. Thus, the Sry protein points an indifferent embryo toward maleness and the maintenance of testosterone production. The sex switch initiates a developmental sequence involving numerous genes. Eva Eicher and Linda Washburn have developed a model in which two pathways of coordinated gene action help determine sex, one pathway for each sex. The first gene in the ovarydetermining pathway is termed *ovary determining* (*Od*).

The first gene in the testis-determining pathway must function before the *Od* gene begins, in order to allow XY individuals to develop as males. Once the steps of a pathway are initiated, the other pathway is inhibited.