

Is there a gene for gender?

Aristotle thought boys were created when their parents made love in a north wind, girls when the wind was from the south. Germanic folklore says to take an ax to bed to beget boys, but leave it in the woodshed to produce girls. After centuries of such creative conjectures, biologists began zeroing in on a more plausible explanation for the origins of the sexes. In a 1988 paper published in the scientific journal *Cell*, researchers led by David C. Page of the Whitehead Institute for Biomedical Research in Cambridge, Mass., reported the discovery of what seems to be a single gene that determines whether a human embryo will be male or female.

Humans have 23 pairs of chromosomes. Researchers have known since 1959 that gender is determined by the pair that consists of an X and a Y (so named because of their shape) in men, and two X's in women (see figure at right). But they have never understood just how the process unfolds. In rare cases, men have two X chromosomes and women have an X and Y. These exceptions to the rule are sterile or infertile, but otherwise appear relatively normal. Page and his collaborators studied such natural curiosities. They discovered that one male with two X chromosomes also had a fraction of a percent of a Y chromosome. Just this tiny bit of the Y was enough to make him a man. To firm up their suspicion that this single portion of the Y chromosome determines sex, the researchers studied the chromosomes of an XY woman. They found that her Y chromosome was incomplete: it lacked just the crucial 0.2 percent that would have made her a *him*.

After pinpointing the location of this one powerful snippet, which they call “**testis determining factor gene**,” or **TDF**, Page’s team worked out the biochemical coding that reveals what the gene actually does. According to Page, TDF seems to act as a master switch, “regulating the activity of other genes.” These others, still to be identified, may well include not only genes that shape the body but also those that sculpt the brain, making men’s gray matter different from women’s. Now researchers are trying to find these other crucial pieces of genetic material, hoping to fill out the rest of the age-old puzzle of sexual differentiation.

[From *Newsweek* magazine: January 4, 1988]

Updates to this story:

Although the Page lab’s research narrowed the location of the TDF to a small region of the Y-chromosome, it did not identify the specific gene (or genes) in this region that was in fact the TDF. In 1990, Sinclair and colleagues narrowed the region to a 35,000 base-pair domain of the small arm of the Y chromosome. The further history of finding the locus of the TDF is seen in Figure 3.

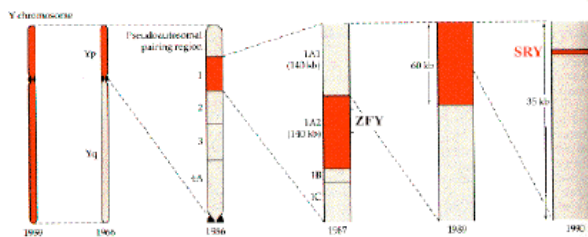


FIGURE 3. In 1959, the Y chromosome was shown to contain the testis determining factor in both humans and mice. By 1966, translocations and deletions of human chromosomes indicated that the TDF resides in the short arm of the Y chromosome (Yp). In the late 1980s, deletion mapping with male-specific DNA probes showed that the gene(s) resided in region 1 of the small arm of the Y chromosome. Studies of XY females, XX males, and transgenic mice have localized the TDF to a single region on the Y chromosome containing the SRY gene. (After McLaren, 1990.)

Some controversy continued through the late 1980s and into the 1990s,



Male sex chromosomes. Colored scanning electron micrograph (SEM) of human X (center) and Y (upper left) sex chromosomes. Each chromosome has replicated to form two identical strands (chromatids). The area linking the chromatids is the centromere. The sex chromosomes inherited during fertilization determine a person’s gender. Males have an X and a Y chromosome (as seen here), whilst females have two copies of the X chromosome. The Y chromosome carries instructions for the development of male characteristics. The sex chromosomes are one pair of 23 pairs present in most cells in the body, which contain the DNA necessary for growth and development. Magnification: x7150 at 6x7cm size. Credit: Andrew Syred / © [Photo Researchers, Inc.](#)

eventually arriving at the conclusion that the SRY gene, which produces a transcription factor (a protein that binds to the DNA molecule in specific places, and causes it to bend sharply, changing the three dimensional geometric structure of DNA and altering the action of a range of other genes), was the TDF.

Research continues to develop in this area and work published in 2004 suggests that SRY may not be the be-all, end-all TDF as other developmental genes may control SRY expression. New data suggests that genes in the insulin receptor tyrosine kinase family, which are found upstream of SRY on the Y-chromosome, are required for male sexual differentiation in mice.

- Developmental genetics: the Making of a Male.
- Determining the Human TDF locus - how did we figure out where the TDF was located?
- Genetic evidence equating SRY and the testis-determining factor.
- Human sex determination.
- The development of sexuality.

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