

Sex-determining Region Y in Mammals

The Sex-determining Region Y (Sry in mammals but SRY in humans) is a gene found on Y chromosomes that leads to the development of male phenotypes, such as testes. The Sry gene, located on the short branch of the Y chromosome, initiates male embryonic development in the XY sex determination system. The Sry gene follows the central dogma of molecular biology; the DNA encoding the gene is transcribed into messenger RNA, which then produces a single Sry protein. The Sry protein is also called the testis-determining factor (TDF), a protein that initiates male development in humans, placental mammals, and marsupials. The Sry protein is a transcription factor that can bind to regions of testis-specific DNA, bending specific DNA and activating or enhancing its abilities to promote testis formation, marking the first step towards male, rather than female, development in the embryo.

In humans the first step in the development of an organism's sex is the inheritance of an X chromosome from the mother, and either an X or Y chromosome from the father. Typically, an XX individual develops as a female and an XY individual develops as a male. Studies by University of Kansas zoologist Clarence Erwin McClung in Lawrence, Kansas at the turn of the twentieth century helped researchers focus on the roles of chromosomes for sex determination. McClung theorized that there were two distinct types of spermatozoa, each of which resulted in different forms of fertilized eggs, leading to either male or female development. Nettie Maria Stevens, a post-doctorate researcher at Bryn Mawr College, located near Philadelphia, Pennsylvania, expanded upon McClung's theory in 1905, observing that spermatozoa are of two distinct forms, containing either an X or a Y chromosome. Based upon her research on sex determination in insect species, Stevens concluded that the Y chromosome carries the genetic material that leads to male development.

Stevens's work identified the Y chromosome as a heritable structure that somehow caused sex determination in the embryo. Her results supported the theory proposed in the early 1890s by zoologist researcher Walter Sutton at Columbia University in New York City, New York and biologist Theodore Boveri at University of Würzburg in Würzburg, Germany, that chromosomes contain genetic material. At that time, however, researchers couldn't detail the mechanism through which chromosomes work to induce changes in the cell. Experiments conducted by Frederick Griffith in 1928 at the Ministry of Health in London, England confirmed the existence of a factor in cells capable of transferring genetic information.

In 1944 Oswald Avery, Colin Macleod, and Maclyn McCarthy, at the Rockefeller Institute for Medical Research in New York City, New York, discovered that chromosomes contain DNA, the molecule that encodes an organism's genetic information. The discovery of DNA's structure in 1953 by James Watson and Francis Crick at the Cavendish Laboratory in Cambridge, UK enabled researchers to develop biochemical technologies, such as Polymerase Chain Reaction, which can replicate a single DNA sequence several million times. These techniques enabled researchers to describe the mechanisms that underlie developmental pathways, including the role of SRY gene in sex determination.

Starting in the early 1980s, research teams in London, UK led by Robin Lovell-Badge at the National Institute for Medical Research and Peter Goodfellow at the Cancer Research UK London Research Institute sought to identify the genes present on the Y chromosome that induced male development. Scientists first scanned the Y chromosomes of several mammals for the presence of genes involved in testis formation. The scientists claimed that the gene would encode for the testis-determining factor (TDF), a protein responsible for causing testis to develop in embryos. The team found a sequence on the Y chromosomes of several species of mammals. The transcripts from those sequences were all found only in testes. The gene, designated the Sex-determining region Y, provided a candidate

for expression of the TDF.

Confirmation of the Sry gene encoding the TDF came from several experiments that focused on mutations in the SRY gene. Early evidence came from research conducted by Peter Goodfellow and his teams at both the Cancer Research UK London Research Institute and the National Institute for Medical Research in the late 1980s and early 1990s. That research showed that mutations in the Sry gene halted the embryonic development of testes, resulting in organisms that possessed a Y chromosome but expressed female phenotypic characteristics. Robin Lovell-Badge and her team at the National Institute for Medical Research later confirmed Sry gene's role in sex determination in an experiment where researchers injected Sry gene sequences into chromosomally female (XX) mice embryos during early embryonic development, and the embryos developed into males.

Throughout the 1990s, several researchers argued that Sry protein acted directly upon the genital ridge, the region in early embryonic development from which either the ovary or the testis form. Researchers assumed that Sry protein helped change epithelial cells into Sertoli cells. Sertoli cells are only in males and produce key proteins and hormones during male development. However, later scientists argued that SRY protein indirectly induces mesonephric cells to migrate into the genital ridge. SRY protein causes cells in the genital ridge to secrete a chemotactic factor that causes cells from the adjacent mesonephros to migrate in to the genital ridge. The mesonephric cells, rather than SRY protein directly, induce the genital epithelial cells to become Sertoli cells.

Researchers have linked mutations in the SRY gene to forms of sex reversal. One example is Swyers syndrome, a condition in which a person who has XY sex chromosomes develops the physical characteristics of a female. Mutations in the SRY gene account for between fifteen to twenty percent of cases of Swyers syndrome. Additionally, the presence of SRY gene in genetically XX individuals results in XX male syndrome. This state often results from improper crossing over between X and Y chromosomes during meiosis in the father, resulting in the presence of SRY gene sequences in X chromosomes.

Sources

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