

"Genetic Evidence Equating SRY and the Testis-Determining Factor" (1990), by Phillippe Berta et al. [1]

By: Cox, Troy Keywords: [Sex-Related Gene On Y](#) [2] [Sex Determination Processes](#) [3] [testis-determining factor](#) [4]

In the late 1980s, Peter Goodfellow in London, UK led a team of researchers who showed that the SRY gene [in humans](#) [5] codes a protein that causes [testes](#) [6] to develop in embryos. During this time, scientists in London and Paris, including Peter Koompan and John Gubbay, proposed that SRY was the gene on the Y chromosome responsible for encoding the testis-determining factor (TDF) protein. The TDF is a protein that initiates embryo to develop male characteristics. Looking for evidence that SRY was the TDF, Goodfellow and colleagues examined people who were anatomically female, but whose cells had Y chromosomes. Females normally have cells with two X sex chromosomes (XX), while males normally have cells with one X and one Y chromosome (XY). Goodfellow's team discovered that individuals with Y chromosomes developed as female instead of as male due to inactive SRY sequences on the Y chromosome. Goodfellow and colleagues compiled the results of their experiment in a paper titled "Genetic Evidence Equating SRY and the Testis-Determining Factor" in 1990. Their results showed that the SRY gene is necessary for male characteristics to develop in embryos, and that SRY encodes the TDF protein.

Goodfellow and his colleagues conducted their research at Lincoln's Inn Fields laboratories in London, UK. The team, which included Goodfellow, Phillippe Berta, J. Ross Hawkins, Andrew Sinclair, Anne Taylor, and Beatrice Griffiths, collaborated with Marc Fellous at the Institut Pasteur in Paris, France. Goodfellow had conducted research on the SRY gene throughout the 1980s at the Laboratory of Eukaryotic Molecular Genetics at the National Institute for Medical Research at London, UK. Initially, researchers identified the SRY gene by sequencing regions of the Y chromosome in organisms from different species of mammals. Researchers found that the gene was highly conserved, or present with few to no changes, in the Y chromosome of several species of mammals. Using this data the team theorized that the gene somehow caused male embryonic development. To confirm this theory, Goodfellow and colleagues chose to examine inactive SRY [genes](#) [7] that resulted in chromosomally XY human females.

To determine the role of the SRY gene in the development of sex characteristics, Goodfellow's team studied two people that were genetically XY but had the physical characteristics of women. The team amplified SRY gene sequences from regions of the Y chromosome of the two XY females, who were referred to as AA and JN, and from fifty XY males using polymerase chain reaction (PCR). Polymerase chain reaction allowed the team to copy and amplify the original gene sequences, and from that copy to make additional copies. The male sequences were used to identify sequence similarity in normally developed males and to contrast this information with the sequences obtained from the XY females. SRY gene sequences were also obtained from the fathers of the XY females as well as the brother of AA to compare with the sequences of the XY females, as the Y chromosome is always inherited from the father.

Goodfellow's team cut the SRY gene sequences with restriction enzymes, enzymes that cleave DNA at specific recognition sites, to analyze the sequences. The team used polyacrylamide gel electrophoresis, which sorts DNA sequences by length through a gel matrix using electricity. Goodfellow's team analyzed the length of the sequences to determine if there were significant changes in the size of the strands from the XY females compared to the XY males. The team also examined the DNA sequences of the SRY strands and looked for genetic differences present in the SRY sequences of the XY females. The researchers observed three trends: a pattern common to all fifty normal males, a pattern specific to AA, and a pattern specific to JN.

Of the fifty males analyzed, all contained identical SRY gene sequences. The result confirmed the claim that unaltered SRY gene sequences typically result in normal male development. Goodfellow and the researchers found that in the XY female, AA, the genetic sequence had a transition; a change in a single DNA nucleotide base from a guanine to adenine. That change in nucleotides resulted in the construction of the amino acid isoleucine instead of methionine during gene expression. The change in a single amino acid created a non-functioning protein product from the SRY gene. This genetic change was present only in AA and was not present in her father or brother. The team concluded that a *de novo mutation*, a mutation that is not present in or passed from either parent, had occurred. Goodfellow's finding showed that a mutation in the SRY gene of AA resulted in abnormal function of the SRY gene, ultimately causing AA to develop female characteristics.

Analysis of JN, showed a transversion, a base change from guanine to cytosine, in her SRY sequence resulting in the amino acid leucine rather than valine. This change was also present in the sequence provided from her father, however, her father developed as a male. Goodfellow's team suggested that the father contained other genetic factors that were not impaired by the base change. The team concluded that the father was also likely mosaic, meaning that cells within his body contain different genetic sequences. In this case, the team predicted that the cells of JN's father likely contained varied SRY sequences, many of which were functional. Because the same mutation was found in both JN and the father, Goodfellow's team could not confidently

state that the mutation was the cause of the development of female characteristics in JN.

The experiment showed that a *de novo* mutation in the SRY gene can cause an embryo with XY sex chromosomes to develop as a female. The change in a base pair, and consequently amino acid, caused a non-functional protein product leading to female, rather than male development. Goodfellow's research supported the claim that the SRY gene encodes the testis-determining factor in [humans](#)^[5] by highlighting genetic differences of typical male SRY sequences and that of XY females.

Sources

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Subject

[Testis](#)^[10] [Y chromosome](#)^[11] [Embryos](#)^[12] [Chromosomes](#)^[13] [Sex chromosomes](#)^[14] [Sex determination, Genetic](#)^[15] [Sex differentiation](#)^[16] [Human chromosomes](#)^[17] [Koopman, Peter](#)^[18] [Genes, sry](#)^[19] [Sex-Determining Region Y Protein](#)^[20] [Y Chromosome](#)^[21]

Topic

[Experiments](#)^[22]

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- [2] <https://embryo.asu.edu/keywords/sex-related-gene-y>
- [3] <https://embryo.asu.edu/keywords/sex-determination-processes>
- [4] <https://embryo.asu.edu/keywords/testis-determining-factor>
- [5] <https://embryo.asu.edu/search?text=humans>
- [6] <https://embryo.asu.edu/search?text=testes>
- [7] <https://embryo.asu.edu/search?text=genes>
- [8] <https://embryo.asu.edu/search?text=Developmental%20Biology>
- [9] <https://embryo.asu.edu/search?text=Homology>
- [10] <https://embryo.asu.edu/library-congress-subject-headings/testis>
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- [13] <https://embryo.asu.edu/library-congress-subject-headings/chromosomes>
- [14] <https://embryo.asu.edu/library-congress-subject-headings/sex-chromosomes>
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