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# The tenuous nature of sex

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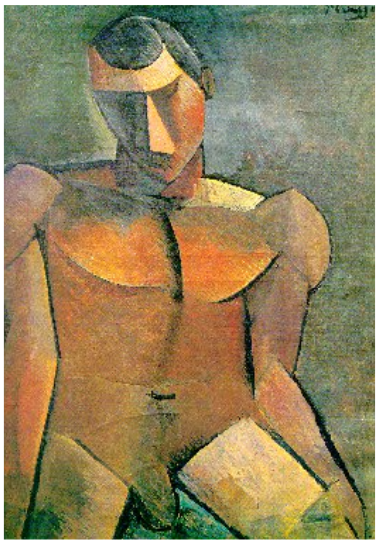
**Everyone knows how to tell the difference between a boy and a girl. The exterior signals are obvious. And yet, despite such a clear statement on Nature's behalf, the molecular pathways underlying our being either male or female are subtle and fragile. It takes very little to make a woman out of a man – at least as far as our chromosome makeup is involved. We were told that boys are XY, and girls XX. But it's not so simple. Some girls are XY, and some boys are XX… So there must be something sophisticated involved. And we are only beginning to discover what. Because of its singular architecture, the male Y chromosome is distinctive under the microscope and it was not long before 19th century scientists caught on that it had a major role in the making of a man. A closer look at it led molecular biologists to a specific region on the Y chromosome and, in the 1990s, scientists announced the discovery of a protein – the Sex-determining region Y protein (Sry) – that had a major role in convincing a foetus to become a baby boy.**



Seated Male Nude, Picasso (1909)



How an embryo becomes male or female has puzzled many a human for thousands of years. While menstrual blood was believed to be the material with which semen moulded the beginnings of a foetus, it was thought that heat favoured the development of little boys and cold shaped an embryo into a little girl. Semen that came from the right testicle gave boys; the left testicle harboured the wherewithal to make girls. Likewise, embryos that were positioned to the right of the womb became male, and those to the left, female. Once the notion of two germ cells and their meeting was acknowledged, the Ovists believed that a child was held within an egg and just needed sperm to trigger off its development, while the Spermists speculated that it was sperm that sheltered the embryo, and the egg was there to feed it. As time passed and techniques improved, scientists discovered not only chromosomes but also the fact that specific chromosomes defined sex. The X chromosome was the first to be discovered because of its size. Y was discovered shortly after.

The fate of the Y chromosome is bewildering. It all started 300 million years ago when Nature thought up sexual reproduction. To reproduce in this way, you need at least two entities of an opposite sex. It was a great way to promote biological diversity and a basis on which natural selection could work, but it meant compromising on one chromosome, i.e. the Y chromosome as we know it today. 300 million years ago, a large portion of an X chromosome was inverted. As a consequence, it was unable to pair with its sister chromosome. Left to fend for itself, it fast became prey to mutations and over the years it has lost hundreds of genes, gained a lot of rubbish and become very small. So much so that some scientists think that the Y chromosome may just wither away…and hence the male of the species? 'Nonsense!' say fellow researchers, other animals have lost their Y chromosome already and have simply found another way of promoting the male program. There is no reason why *Homo sapiens* wouldn't do the same, and some of the future mutations on Y may even support its survival.

So as long as XY embryos carry Sry, their destiny is a male one. What does Sry do? It triggers off pathways that promote the development of masculine features which depend upon two types of

cell: the Sertoli and the Leydig cells. Sertoli cells give rise to the testes and Leydig cells will ensure the production of androgens - the male hormones. How does Sry do this? Sry is a transcriptional factor and binds to the minor grooves of DNA. There – by way of bending the nucleotide structure at angles of 60 to 80° – it either activates or represses the transcription of genes. To date, no one is sure whether Sry activates 'male' genes or whether it represses 'female' genes – though there is growing evidence for the former. Naturally, Sry does not act on its own; without the help of molecules both upstream and downstream of Sry expression, there would be no baby boy at all – or one whose male features are hugely hindered.

Up until the 7th week of pregnancy, a human embryo's phenotype is neither male nor female. If the embryo is XY, Sry is expressed – though only for a short time. In mice, for instance, Sry is active from the 10th day of development until the 12th day. And if it misses the bus, the embryo is heading for serious trouble. In fact, problems related to a person's sex can be the cause of a dysfunctional Sry, either because it has not been expressed, because it is inactive or because it wasn't expressed on time. Besides its role in sex differentiation, Sry is also found in male brains. Could it be involved in what could be described as 'male' behaviour? Possibly. It seems to have a role in the production of dopamine which is involved in motor control. The obvious question then is: are women handicapped in this respect? Of course not. In fact, the female hormone oestrogen also has a role in dopamine production and could replace that of Sry...

It takes a network of molecules to become a boy or a girl. Sex is not the work of only one protein though Sry is certainly sitting on a hinge. Integrated into an XX mouse embryo, it can switch the sex program and a female mouse becomes…male. Mice are not human though. Furthermore, the common belief that girls only become so because Sry is not expressed, is not accurate. Women are not passive in their making. One of Sry's doings is to activate the production of a hormone known as AMH which ensures that any feminine features are impeded.

To cut a long story short, the chromosomal definition of a man is XY, and that of a woman XX. But it takes very little to confuse the nature of one or the other by providing our species with humans that carry both feminine and masculine attributes for example, or by 'turning' what 'should' have been males into females, or females into males. There are XY females where Sry is not expressed and XX males where Sry is expressed thanks to the presence of its gene on an X chromosome. And there are hermaphrodites whose phenotype is neither male nor female, but a bit of both. The making of a sex is not a trivial affair and we should bear in mind that it takes very little to tip the scales and confuse the program. It is a thin line between a man and a woman.

## Cross-references to Swiss-Prot

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