

that are more credible than currently available projections. ■

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In retrospect

Twenty-five years of the sex-determining gene

The discovery that the gene *SRY* on the mammalian Y chromosome drives testis development marked a turning point in the decades-long quest to understand the genetic underpinnings and evolution of sex determination.

JENNIFER A. MARSHALL GRAVES

It has long been known that a testis-determining factor (TDF) on the Y chromosome kick-starts testis development in humans and other mammals. The testes make hormones, and these hormones make the embryo male. Twenty-five years ago, Sinclair *et al.*¹ reported in *Nature* that TDF was the gene *SRY*. This discovery opened up the surprisingly intricate genetic pathway that determines whether a baby is born a boy or a girl. It also led to an understanding of how genes on the Y chromosome evolved, and of the impact of this key evolutionary event.

Until the 1980s, there was no viable candidate sex-determining gene. Just where was TDF located? What kind of product did it encode? What did it do? During the 1980s, the position of TDF was narrowed down to a small region on the short arm of the Y chromosome, when it was found that some males had XX chromosomes that harboured a small piece of the Y, whereas some females had XY chromosomes that lacked bits of the Y — these added and deleted regions of Y were assumed to contain the TDF sequence. The race was then on to find TDF.

In 1987, the geneticist David Page and his associates² identified the first coding gene on the human Y, called *ZFY*. The gene looked like a winning candidate: it was in the right place; it was expressed in the testis; and it was evolutionarily conserved in other placental mammals, such as monkeys, mice, dogs and horses. But in 1988, PhD students in my laboratory³, Andrew Sinclair and Jamie Foster, mapped *ZFY* to a non-sex chromosome (an autosome) in marsupials, which are a separate branch of mammals. A few months later, it

was found⁴ that, although *ZFY* is expressed in mouse sperm precursors, it is absent from the other cells of the testis, where a true TDF must be expressed to exert a sex-determining effect.

Sinclair joined a renewed hunt for human TDF in the laboratory of geneticist Peter Goodfellow, using DNA from XY males that had even smaller pieces of the Y than had previously been studied. This was slow and frustrating work, because the Y chromosome is full of repetitive sequences and so specific regions are hard to pinpoint. It was 1990 before they found¹ a small coding gene close to the end of the Y chromosome (Fig. 1). Noncommittally they called the gene *SRY*, for sex region on the Y. The final proof that *SRY* was the TDF came from the discovery of *SRY* mutations in XY females⁵ and from the demonstration that adding *Sry* to XX mice was sufficient to induce male development⁶. *SRY* was located on the Y in other placental mammals and, thankfully, even in marsupials⁷.

Researchers in the field imagined that identifying TDF would rapidly lead to an understanding of how it worked, and would point to other genes in the sex-determining pathway. But 25 years on, it has become clear that the pathway kick-started by *SRY* is complex, full of checks and balances.

Initially, *SRY* proved a puzzle because it was unlike any known gene. It turned out to be a member of a previously unidentified family, now called the SOX genes. Painstaking biochemical studies of the *SRY* protein revealed that it bound to a certain DNA sequence and bent it at an angle, presumably to bring other sequences — or the proteins bound to them — into proximity, promoting or inhibiting transcription⁸. The discovery of a different



50 Years Ago

The Royal Society Anniversary Address by Lord Florey, O.M., P.R.S. Perhaps the deployment of Government resources is the modern equivalent of events in the early days of the Society when Fellows contributed—or sometimes did not contribute—a shilling a week towards demonstrating experiments at meetings. There never was enough money... At the moment it is considered to be desirable to give free medicine to all. The application of free calamine lotion to the irritated skins of the populace may be more important than administering to the needs of irritated scientists; but this sort of judgement is in the realm of politics... it has long been the policy of the Society to have symposia and lectures... the popularity of such gatherings has brought difficulties... on one occasion, we had to migrate to the lecture theatre of the Shell Building on the South Bank... one consequence of this peripatetic existence has been that we have had to procure a coffin-like box for the transport of the mace, and I am sure that our original Fellows, and even Charles II himself, might have been somewhat astonished at the adventures of their royal emblem.
From *Nature* 18 December 1965

100 Years Ago

The Romanes Lecture... was a scathing indictment of the ineptitude of the lawyer-politicians who possess a dominating influence on national affairs... To the neglect of science, and the excessive predominance in Parliament and the Government of men with the spirit of the advocate to whom all evidence which will not support their case is unwelcome, Prof. Poulton ascribes the chief mistakes in the conduct of the war.
From *Nature* 22 November 1915