

## The Gene That Makes a Man a Man

*The Mammalian Y Chromosome: Molecular Search for the Sex-determining Factor*, 1987. Edited by P. N. GOODFELLOW, I. W. CRAIG, J. C. SMITH and J. WOLFE. Supplement to *Development*, vol. 101, Company of Biologists, Pp. 203. £35, \$60.

By Lee M. Silver

In March 1987 the British Society of Developmental Biology held a meeting devoted to the mammalian Y chromosome and its role in sex determination. The proceedings of this meeting were published in a handsome monograph that documents a scientific race still in progress, but with a finish line clearly in sight. One need look no further than the cover of this volume, with a reproduction of a Raphael drawing of a naked young boy, to see the quest of the competing players – the cloning of the gene that ‘makes a man a man’ – the *testis determining factor* (*TDF* in man, *Tdy* in mice). Aside from an intrinsic interest in sex determination, the excitement in this field stems from the fact that *TDF* is one of the few (some would say only) well-defined mammalian genes known to have a master regulatory role in embryogenesis. The hope is that *TDF* could lead the way towards an understanding of general principles involved in the genetic control of mammalian development. It is clear that by the spring of 1987, ‘the stage (was) set’, as Goodfellow says in the introduction, for a major breakthrough.

Three very different types of mechanism have been utilized to produce sexual dimorphism in different species of animals. One involves the expression of sex chromosome-linked dominant genes like *TDF*; a second is based on the ratio of *X* chromosomes to autosomes in the genome; a third involves environmental rather than genetic signals. The first two papers in this monograph provide lessons to be learned from the study of organisms,

such as *C. elegans* and *D. melanogaster*, where chromosomal ratios are normally used to determine sex. Through the powerful genetic tools available in these systems, it has been possible to create: (1) *C. elegans* mutants that determine sex according to a *TDF*-like system, and (2) flies that determine sex according to environmental temperature. As McClaren states in the introduction to this set of papers, ‘the underlying logic of sex-determining mechanisms may have been conserved in evolution even though the details ... may change rather rapidly’.

The remaining papers are focused on the Y chromosome in mice and men. Seven papers discuss pseudogenes and genes other than *TDF* found on the human Y chromosome. Three papers describe various repetitive DNA sequences on the human Y and another four papers describe studies of the Y chromosome and autosomal genes involved in sex determination in mice. De la Chapelle provides suggestive evidence for the existence of an autosomal dominant mutation that causes the production of at least some testicular tissue in XX individuals that appear to completely lack Y sequences. If true, this finding would indicate that *TDF* is not absolutely required for testes production in mammals, and it would strengthen the argument for an underlying commonality among all sex determination systems in the animal kingdom.

As I indicated above, the major focus of this monograph was the race to clone *TDF*, and all the major players in this competition are represented. The approach to cloning the gene is straightforward in principle. *TDF* is defined by a clear phenotype, but without the existence of a known gene product. Therefore, cloning must proceed by the ‘reverse genetic’ approach of localizing the gene to the smallest genomic region possible and then searching through clones of this region for properties that one might expect to find associated with a mammalian testes-determining gene.

Regional localization of *TDF* on the Y chromosome can obviously not be accomplished by classical recombination analysis. Instead, investigators have utilized rare patients (some of whom develop testes and some of whom do not) that carry only fragments of the Y chromosome to perform deletion mapping with sets of Y-specific DNA probes. A number of papers in this volume are directed towards studies in this critical area.

At about the time that this monograph was being printed, the race for *TDF* came to an end with the publication by David Page and his colleagues describing the complete cloning of the *TDF* region with a very strong candidate for the gene itself (Page *et al.*, *Cell* **51**, 1091–1104). The Page paper was particularly satisfying in that the predicted amino acid sequence has properties characteristic of a DNA-binding protein – precisely as one might predict for a gene product with a master regulatory function. With clones of *TDF/Tdy* in hand, an understanding of sex determination in mammals is clearly within reach.

It is a pity that this Symposium on the Y chromosome was not held a year later, when it would have included not only a description of the search for *TDF* but also a description of the gene itself. In this light, the monograph is truly an example of a scientific publication that was outdated before it was published. Nevertheless, the book still serves an important purpose in providing a single, well-organized source for the background studies essential both to the ultimate cloning of *TDF* and to the understanding of the role played by *TDF* and other genes in sex determination. Furthermore, this book provides a feeling for the excitement and competition present in a scientific field just before the dawn of a new era.

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