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2 When Gender Criticism Becomes Standard Scientific Practice

The Case of Sex Determination Genetics

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THIS CHAPTER DOCUMENTS the contribution of gender analysis to the field of sex determination genetics. The cloning of the *SRY* (sex-determining region of the Y chromosome) gene in 1990 appeared to confirm a long-standing model of genetic sex determination—that of a single "master gene" on the Y chromosome that directs the development of the male gonads and thereby determines sex. By the late 1990s, however, this model fell as a result of challenges from all sides, including gender criticism. Today, the *SRY* gene is understood as one among many essential mammalian sex-determining factors involved in the genetic pathways of both testicular and ovarian determination. Mammals require cascades of gene product in proper dosages and at precise times to produce functioning male and female gonads, and researchers recognize a variety of healthy sexual phenotypes and sex determination pathways in humans.

What part did gender analysis play in this remarkable transformation in models of sex determination? In what follows, I document how gender criticism became a cognitive resource in the field of sex determination genetics during the 1990s and contributed to the development of a significantly revised genetic theory of sex determination. It contributed in at least three ways. First, feminist biologists and science analysts anticipated the revised model earlier than others. Second, feminist theories of sex and gender lent intellectual resources to the model reconstruction effort. Third, gender criticism sharpened the epistemic tools of the field of sex determination

genetics. It improved the level of critical discourse about the assumptions, language, and interpretive models of the field, and provided an analytical framework for articulating and making visible previously unattended gaps in knowledge.

Developments both internal and external to the field facilitated the acceptance of gender criticism in the standard critical practices of sex determination research, a process I call "normalization of gender criticism."[1] I identify three stages in the progressive incorporation of gender criticism into sex determination genetics. First, cultural change in and around the field of sex determination genetics created the conditions for receptivity to gender criticism, including early feminist criticism from outside the field. Second, a respected female scientist in the field, Jennifer Graves, began to employ an explicitly feminist framework in her work. Graves introduced feminist criticism to the field and developed a formidable gender-critical alternative model of sex determination genetics. Third, over time, members of the larger sex determination research community came to see gender criticism as useful to their own thinking, incorporating feminist insights even while often not explicitly articulating them as such. In this way, gender criticism became a part of the mainstream critical practices of the field.

SRY, the Sex-Determining Gene

In 1959, analysis of human intersex individuals demonstrated that the genetic switch for male sex determination is located on the Y chromosome. It was not until the mid-1980s, however, when technologies for cloning, sequencing, and analyzing the human genome became cheaper, faster, and more ubiquitous, that a serious gene discovery program was undertaken for the "sex-determining gene." At this time, research groups at Massachusetts Institute of Technology in the United States, the National Institute for Medical Research, Medical Research Council, and Imperial Cancer Research Fund in London, and La Trobe University in Australia began competing to analyze the Y chromosome and clone the sex-determining gene.

The sex-determining gene became a high priority target in the early days of human genetic sequencing for several reasons. First, sex determination appeared to present a model system in which a single "master gene" controlled the development of an entire organ system. As geneticist Edward Southern wrote in 1987, "Sex determination, as a model for the developmental process

in mammals, is undoubtedly the principal reason for the intense activity of research on the Y chromosome" (Goodfellow et al. 1987, 75).

The sex-determining gene was also a low-hanging fruit. The Y chromosome is many times smaller than the other twenty-three chromosomes and houses only a few genes; it is a comparatively tractable target for genetic analysis. Through recombinant technology and deletion analysis in the 1970s, researchers had already isolated the sex-determining gene to a small region of the Y chromosome. Rapid sequencing technologies and straightforward micro-level deletion analysis of the Y chromosome of intersexed mice and humans promised to reveal the location of the crucial switch. As leading geneticist Peter Goodfellow of the Imperial Cancer Research Fund in Britain wrote in 1987, "the stage is set for cloning the mammalian sex-determining gene" (Goodfellow et al. 1987, 1).

Finally, the male sex-determining gene represented a holy grail of sex difference research. Prevailing theory held that two factors control sex difference: a gene triggers gonad differentiation and sex hormones direct the development of the gonads and secondary sex characteristics. Sex hormones having been well characterized by the 1970s, the sex-determining switch would complete the account of the biology of human sex differences. Thus, the male sex-determining gene was a prestigious prize, a long-sought theoretical breakthrough that promised to answer persistent questions about male and female sex difference and found a new field of research.[2]

The genetic search for the male "sex-determining factor" began in earnest in 1986 (Wilkie 1991). Researchers used mouse models to probe a sex-determining region of the Y chromosome isolated from intersex patient karyotypes. In 1987, David Page, a researcher at MIT and the Whitehead Institute in Boston, announced that a gene called *ZFY* satisfied the criteria for the sex-determining gene (Page et al. 1987). Within a year, Australian researchers Jennifer Graves and Andrew Sinclair overturned the finding. Sinclair went on to identify the *SRY* gene for male gonad formation in 1990 (Berta et al. 1990). In 1991, accompanied by a *Nature* cover with the "star mouse, swinging on a stick and sporting enormous testicles to prove the point," Goodfellow, Peter Koopman, and Robin Lovell-Badge confirmed the sex-determining role of *SRY* by showing that a transgenic XX mouse would develop as a male if *SRY* is appended to one of the X chromosomes (Koopman et al. 1991; Sykes 2003, 71). Following on the heels of this work, in 1992 Page published the first genetic map of the Y chromosome (Vollrath et al. 1992).

The *SRY* model of sex determination confirmed the anticipated model of sex determination controlled by a single "master gene" on the Y chromosome. Media coverage of the discovery of the *SRY* added to the hype: "scientists now think they know what makes a male masculine," trumpeted the *New York Times*; "scientists believe that they have at last unraveled the secret of what makes a man," announced the *Guardian* (Angier 1990; Williams 1990). The scientific community celebrated *SRY* as an example of "the astonishing power of modern molecular techniques to resolve long-standing and difficult questions in genetics with consequences that extend far across biology" (Williams 1990). Textbooks immediately incorporated the *SRY* gene into accounts of sex determination. In 1992, the International Olympic Committee added a test for the *SRY* gene to its "gender verification" program for female athletes.

A Changing Public Discourse About Gender and Science

The 1980s initiated a period of intense public debate about gender and science. The NIH Office of Research on Women's Health opened its doors in the early 1990s, raising the profile of women's and gender issues in American science. This period also witnessed significant expansion of feminist science studies pedagogy and scholarship in the academy. In research biology, particularly genetics and developmental biology, women entered the profession in numbers that for the first time approached parity.

In large part as a result of these developments, the 1990s saw increasing challenges to dominant biological models of sex and gender. Biological claims about intersexuality and homosexuality came under particular scrutiny. Feminist science analysts retheorized these phenomena as part of the normal spectrum of human sex and gender. Over the course of the decade this work found its way into sex determination genetics through a variety of channels. The mid-1990s controversy over sex chromosome testing for "gender verification" of female Olympians, ultimately leading to the termination of this practice, provided sex chromosome researchers, whose expertise was sought, with a public crash course in the social impact of scientific definitions of sex and gender (Puffer 2002). The intersex movement also became increasingly visible during the 1990s, emblemized by the founding of the Intersex Society of North America in 1993. Sex chromosome researchers who studied and provided care for intersex and gender dysphoric patients gained exposure to

gender-critical perspectives and were drawn into political and medical advocacy in this community. The "gay nineties" also changed the discursive context and conditions of sex and gender research in biology. The 1990s, for instance, saw the burgeoning of diversity-affirming science writing highlighting the rich variety of sexual life in the natural world, in part a response to dominant assumptions that homosexuality is "unnatural" (see, for example, Bagemihl 1999 and Roughgarden 2004).

An Androcentric "Master Gene" Model of Sex Determination

Sex determination genetics in the 1980s inherited an "androcentric" theory of sex determination from endocrinology. First articulated in 1953 by Alfred Jost, the theory held that humans are bipotential until six weeks after conception, at which time two biological switches initiate sexual dimorphism. First, a gene on the Y chromosome triggers the development of the testes. Second, the testes begin producing two hormones, MIS (Müllerian Inhibiting Substance) and testosterone, which "masculinize" the fetus and initiate hormonal control of sexual development. Jost's 1950s research showed that errors in the development of a genetic male, either at the hormonal or the genetic level, cause mice to "revert" to a female developmental pathway. On this evidence, he hypothesized that the development of female gonads and secondary sexual characteristics is the body's "default" plan. In the absence of the two switches, a fetus will develop ovaries and become a phenotypic female. In 1959, cytogenetic studies of intersex patients by Charles Ford corroborated and extended Jost's view of sexual development. Ford's research established that no matter the number of X's, the presence of a single Y causes male gonads to develop, confirming that the sex-determining switch is located on the Y chromosome.

From Jost and Ford, then, the field of sex determination genetics inherited an androcentric framework for sex determination research: a gene on the Y chromosome initiates testis formation; testis formation is the crucial sex-determining event; and female sexual development proceeds as a "default" in the absence of this gene. This theory led researchers in the early 1980s to focus on isolating the "male-determining gene" on the Y chromosome and to see the question of *sex* determination as the question of the genetics of *male testis* determination.

"Master gene" theories in developmental genetics were the second principal source for 1980s models of sex determination. The search for the sex-determining gene in the 1980s was not, as one might suppose, directed toward medical or "gender verification" applications. Rather, its prospects for validating an emerging approach to general questions in developmental genetics drove much of the early interest in the sex-determining gene. As conference chair Peter Goodfellow wrote in the introduction to a symposium volume on sex determination genetics, researchers' interest in *SRY* at this time was primarily "as a model for genetic control of development in mammals" (Goodfellow et al. 1987, 1).

Sex determination research in the 1980s found kinship with a particular school of developmental biology that modeled developmental processes as genetic hierarchies controlled by "master switches" in the genome. The then prevailing paradigm for genetic control of development, as Goodfellow wrote, "assumes a hierarchy of regulatory genes," "an archetypical regulatory network." "In the simplest case, a master control gene directly regulates secondary genes which, in turn, regulate the expression of other genes" (Goodfellow et al. 1987, 1). Once the "master gene" that triggers this hierarchy is discovered, the identification of other genes involved in the hierarchy should be relatively simple. Assuming that the genes involved in testis determination must be an *important* and fundamental developmental process, such that all mammals would share a single, highly conserved genetic pathway, researchers saw the *SRY* as a perfect "archetype" of this hierarchical system. The aim of this research program was to clone *SRY* in order to build a simple model system for the elaboration of general theories in developmental genetics.

Master gene theories of genetic development, then, formed potent background expectations for sex determination researchers. Researchers showed strong disciplinary allegiance to these theories and were invested in the *SRY* model as proof in principle for their emergent field and research program.

Early Gender Criticism of Sex Determination Models

Anne Fausto-Sterling's "Life in the XY Corral" (1989) is a representative feminist critique of sex determination genetics in the 1980s. In the paper, Fausto-Sterling, a biologist, feminist science critic, and intersex patient activist, analyzed gender beliefs in theories of sex determination and argued that researchers had ignored explanatory gaps in their theories and failed

to consider viable alternative models for sex determination. Her charge was three-fold. First, by equating the genetics of testis determination with the genetics of sex determination, researchers had neglected parallel investigation into the genetics of ovarian development. Second, researchers had privileged male over female processes by accepting a highly resonant metaphor of "male as presence and female as absence." Male processes of sexual development were deemed a more interesting, complex, and dynamic object of investigation than female processes. Third, researchers had assumed that sex organizes into a "clearcut" binary such that it can be unambiguously determined by genetic assay. Fausto-Sterling contrasted these conceptions of sex with feminist and social science concepts of sex and gender. An uncritical commitment to a binary concept of sex, she argued, "led researchers to ignore data which are better accounted for in approaches which accept the existence of intermediate states of sexuality" (326–327, 330).

Fausto-Sterling concluded that these assumptions about gender had "prevented the articulation of a coherent theory" of sex determination. She urged an alternative model of sex determination that includes both male and female developmental pathways and "permits the existence of intermediate states" (329). Fausto-Sterling cited a neglected model of sex determination proposed by Eva Eicher and Linda Washburn that included ovarian development and posited that many genes must interact along complex and overlapping pathways to create male and female gonads (1986). Not a sex determination geneticist, Fausto-Sterling's critique registered little response from specialists. Nevertheless, her alternative model and that of Eicher and Washburn represent an early gender-critical model of sex determination.

The 1990s: Mounting Difficulties with the *SRY* Model of Sex Determination

During the 1990s, the *SRY* model of sex determination encountered serious conceptual and empirical challenges. Jennifer Graves and Roger Short anticipated these challenges in a strong critique issued immediately after the announcement of the identification of *SRY*: "Will all mysteries of sex determination now be revealed? We think not," predicted Graves and Short (1990, 731).

Graves and Short raised several challenges to the *SRY* model of sex determination. First, *SRY* was insufficient to produce a fully sex-reversed, fertile

transgenic mouse, and an X-linked gene was known to override the effect of *SRY* on testis determination (among other empirical anomalies to the *SRY* paradigm). Many more genes, perhaps in distinct pathways, must interact to successfully decide sexual fate. Graves and Short suggested that preference for a Y-chromosomal sex-determining mechanism neglected the role of the X chromosome in sex determination and hypothesized that an X-dosage mechanism may interact with the *SRY* pathway to determine sex.

Second, there was no evidence of a gene target for *SRY* in the early stages of testis formation, suggesting a more circumscribed role for *SRY* in sex determination than the "master gene" and "gene hierarchy" theories presumed. *SRY* need not, as was widely assumed, be a direct, active inducer of testis formation. A more complex and interactive model of sex determination would better account for the lack of a gene target for *SRY*. Graves and Short held that, contrary to expectation, the evidence implicated *SRY* in a double-inhibition pathway. Rather than functioning as an activating switch, *SRY* stops other genes that would inhibit still other genes causing testis development.

Third, Graves and Short challenged the developmental biologists' expectation that sex determination should be well conserved, universal, and nonredundant. They admonished sex determination geneticists to appreciate the diversity of sex determination processes, even among mammals.

In the early 1990s, scientists struggled to interpret research findings inconsistent with the *SRY* model of sex determination. The 1992 Boden Conference on Sex Chromosomes and Sex-Determining Genes, chaired by Jennifer Graves, offers a window into a field in transition as these questions came to a head. In the introduction to the conference volume and transcripts, Reed and Graves (1993) write:

> [W]e are gradually getting *an uneasy feeling* that [the portrait of sexual determination given by Jost] is flawed. The history of studies of sexual differentiation exemplifies the truism to "seek simplicity, then distrust it." . . . *[W]e were not prepared* for the ambiguities and difficulties that would follow in trying to interpret the role of *SRY* in aberrant phenotypes and to ascribe downstream function to its gene product. (1993, x, emphasis added)

Research on *SRY* also confounded researchers' expectations about the biological phenomenon of sex dimorphism in several ways. One was the role of *SRY* in the direct induction of the testis. The conference transcript reveals researchers encountering a lack of fit between the *SRY* model of sex

determination and the data, throwing into turmoil their model-theoretic assumptions and description and interpretation of data:

> CHAIRMAN: But do the transgenic mice tell us that *SRY* is the *only* gene involved in testis determination?
>
> GOODFELLOW: The hoary old question of whether *SRY* can be the sex-determining gene because we know there must be other genes in the cascade, so it can't be the only gene! . . . I find it very compelling that all of the genetic information that you need to make a male is present in that 14kb [of the Y chromosome].
>
> MONK: It *sometimes* makes a male.
>
> BURGOYNE: It only sometimes makes a male, even when it's expressed!
>
> GOODFELLOW: I give up!
>
> (375, identity of "Chairman" (sic) unknown)

Researchers also expected that the sex-determining gene would be well-conserved in mammals such that the sex determination process in mice could then be easily generalized to humans and other species. This expectation (a common assumption when working with model organisms in molecular biology) proved unsustainable in this case.

> CHAIRMAN: [O]ne of the big surprises is how poorly conserved *SRY* is between humans and marsupials.
>
> FOSTER: Yes. We expected *SRY* to be well conserved. . . . We were expecting then—and right up until now—that [*SRY*], being a much more important gene and having a lot more selective pressure on it than any of the average house-keeping genes, would pop straight out and we'd find it on the marsupial Y chromosome. (384)

These and other inconsistencies between expectation and observation reveal, in 1992, a growing frustration with the received model of sex determination. Conference contributors, however, were unprepared at this early stage to formulate an alternative model of sex determination or examine the broader assumptions that structured research in the field.

During the mid-1990s, researchers accumulated more anomalies to the *SRY* model and identified several other important genes in the sex determination pathway. In an early contribution, Ken McElreavey, Eric Vilain, and coworkers at the Pasteur Institute in France reviewed more than a hundred cases of human intersex subjects for whom *SRY* did not offer a sufficient explanation of the phenotype (McElreavey et al. 1993). They hypothesized from these cases that there must be another major factor in sex determination, an "anti-testis" factor, which *SRY* acts to suppress. Opposing a "genetic hierarchy" concept of sex determination, they proposed a "regulatory gene cascade" hypothesis, in which many factors participate in pushing the balance of sex determination in favor of male or female, explaining the observed spectrum of intersex phenotypes.

While articulating a nonbinary vision of the biology of sex and gender, McElreavey and Vilain's hypothesis also picked up on broader conceptual shifts in biology in the 1990s. Simple notions of genetic determinism and gene action increasingly fell short of providing adequate explanations of molecular-level phenomena. By the late 1990s, biologists would move away from metaphors of "master genes" and "genetic programs" and toward nonreductionist, complex regulatory network approaches to biological explanation (see Podolsky and Tauber 1997, Keller 2000, Sarkar 2006).

In another significant mid-1990s finding, researchers identified two species of voles that lacked *SRY* but still reliably produced a fertile male phenotype (Just et al. 1995). This confirmed that *SRY* was neither necessary nor sufficient to produce a male phenotype in all mammals. Comparative genomic evidence that *SRY* is poorly conserved, or highly variable in sequence and target, even between mice, chimpanzees, and humans, and that *SRY* is a relatively recently evolved gene, corroborated this view. These findings suggested that *SRY* may function differently from species to species and also may interact with other sex-determining mechanisms in the genome.

The characterization of the genes *DAX1*, *SOX9*, *DMRT1*, and *WNT4*, all non-Y chromosomal genes that can override *SRY* to cause sex reversal, contributed further to pressures in the late 1990s for a revised model of sex determination. These and others in the expanding docket of genes involved in sex determination increasingly challenged the "master gene" model of *SRY* gene action. A consensus began to emerge that *SRY* was far more "average" than expected, pointing toward a sex determination model of a "cascade" or several cascades of genes working in complex regulatory relation to one another.

Jennifer Graves' "Feminist View" of Sex Determination

Jennifer Graves is a leading scientist and a public figure in Australia, recently tapped to direct Australia's high-profile effort to sequence the kangaroo

genome. A member of the Australian Academy of Science, she has been described as a "National Treasure" (White 2001). Graves is also a rare woman principal investigator in a male-dominated field, as well as a marsupial researcher in a world of mouse models and an Australian with comparatively little public funding in a research environment driven by lavishly endowed American and British labs. As a result, for much of her career Graves was somewhat of an outsider in the field of sex determination genetics.

Graves's specialty is comparative genomics of mammals and marsupials and the genetics of sex chromosomes and sex determination. She is best known for her lab's 1988 work disproving David Page's candidate sex determination gene as the mammalian sex-determining gene (Sinclair et al. 1988). Her critiques of Y chromosome-centric models of sex determination and her "Y chromosome degeneration theory" have made her a figure of some controversy and colorful media attention (Jones 2002; Sykes 2003).[3] As a result, as she said in an interview, "I unexpectedly became a ball-breaking feminist Y chromosome knocker" (White 2001).

Graves did not publicly self-identify as a feminist until her appointment to the Australian Academy of Science in 1999. In papers, talks, and interviews following this, Graves began to place her ideas in a feminist framework. A 2001 profile described her as "concerned that a non-feminist view can [adversely] affect how science is done, particularly in her field that deals with what genes determine sex and sex-related characteristics" (White 2001). One might speculate that Graves's position as an outsider, her enhanced freedom, seniority, and legitimacy following her appointment to the Academy of Science and other honors, rising gender awareness in sex determination research, and frustrating experiences explaining and defending her theories under a media spotlight that insisted on seeing them as contributions to the "sex wars," were enablers and preconditions of her ability and desire to speak from a feminist standpoint—in a profession in which claiming a public feminist identity could be a kiss of death—in 2000.

The 2000 paper, "Human Y Chromosome, Sex Determination, and Spermatogenesis: A Feminist View" presents the clearest elaboration of Graves's feminist critique of the *SRY* model of sex determination. Graves argued that researchers' unreflective assignment of masculine qualities to *SRY* led them to ignore contradictory evidence and prefer an unsustainable model of Y chromosomal sex determination over alternative models. Researchers clung to this model even when countervailing evidence should have led them to

abandon it. Graves termed this the "Dominant Y" theory (667–668). In the paper, she described three principal ways in which this "macho" conception of *SRY* had misled sex determination research (673). She then proposed an alternative model of the Y chromosome and its role in sex determination.

First, Graves argued that the Dominant Y model led researchers to conceive of *SRY* as a transcendent "maleness" gene, a specialized master gene that reflects the ultimate refinement of male sex determination and is ubiquitous in nature. This caused researchers to expect that *SRY* would be well conserved and that it would act uniquely in the first stages of testis formation. Empirical research, argued Graves, showed just the opposite. *SRY* is poorly conserved, shows a weak, inconsistent transcription pattern, and appears to have different functions in different species. Indeed, transgenic experiments demonstrate that the function of *SRY* can be replaced by other genes with a similar structure in the genome (such as *DAX1*). Instead, Graves argued, *SRY* acts as an important switch in sex determination only by a contingency of molecular evolution and possesses no unique qualities or specialty function. *SRY* may very well be a marginal autosomal gene that became integrated into the sex determination pathway by chance when the Y chromosome evolved. Based on the evidence, *SRY* is better conceived, she suggested, as "a degraded relic of a normal gene that just got in the way of another gene" (674).

Second, Graves charged the Dominant Y model with uncritically attributing aggressive and agentic qualities to *SRY*. For instance, researchers presumed a model of Y chromosome evolution in which *SRY* "specialized" over time into a male-advantageous, and possibly female-antagonistic, gene—a result of a genetic sex war. A desire to see *SRY* in this light, she argued, led researchers to overlook the extent to which genes on the Y chromosome, including *SRY*, have homologues on the X chromosome, of which they are often merely degraded versions. The agentic Dominant Y model also led sex determination geneticists to assume that *SRY* acts as an "activator" at the top of a linear hierarchy. Wrote Graves, "This dominant action has traditionally been interpreted to mean that [*SRY*] codes for some kind of activator that turns on transcription of other genes in the male-determining pathway" (669). Graves argued that the attribution of the masculine quality of "active" to *SRY* prevented researchers from imagining more complex models, or models in which the *SRY* gene serves as an inhibitor, "a spoiler that turns off genes" (674), a model now strongly suggested by current research. Some models of *SRY* action went further, attributing the *SRY* gene with the ability to "overrule" genes

in the ovary determination pathway. Once again, as Graves noted, this assumption was later contraindicated by empirical research documenting many examples of genes that can counteract the action of *SRY*, leading to sex reversal of normal XY individuals.

Third, as Fausto-Sterling had some ten years earlier, Graves identified the Dominant Y model as androcentric, devaluing and neglecting female biological processes, leading to explanatory gaps in the theory of sex determination. For example, singular emphasis on the role of the Y chromosome in sex determination caused researchers to overlook or underrate potential contributions from the X chromosome, despite the prominence of X chromosome dosage mechanisms of sex determination in many other species and the discovery of a crucial sex-determining gene on the X chromosome. The genetic pathway of ovarian determination is also neglected. As Graves pointed out, no biological argument is offered for the assumption that ovarian development is a "default pathway"—certainly ovarian development is just as interesting, contingent, and complex as testis development. "[T]here are likely to be just as many genes required for ovarian differentiation and egg development, and so far we know rather little about these genes or how they are switched on in the absence of testis development" (667), she wrote.

A simpler and more explanatorily powerful model, Graves suggested, conceives of *SRY* as a degraded version of a gene on the X chromosome that occupies the role of a genetic switch in sex determination because it happens to be located on a male-exclusive chromosome. Graves emphasized that the genome may contain many genes redundant to *SRY* as well as alternative mechanisms of sex determination, which may involve the X chromosome and may interact with and overlay the *SRY* pathway. For Graves, sex determination is a highly contingent, error-prone, and always-evolving mechanism. Polemically (but underscoring her view that gender ideology has favored a masculine view of *SRY* gene action), Graves called her alternative the "Wimp Y" model of Y-chromosomal sex determination.

In this paper, Graves reiterated and built on arguments incipient in her work since her earliest critique of the *SRY* model of sex determination in 1990. It represents the first instance, however, of Graves's identification of her critique of the dominant *SRY* model of sex determination as a feminist one. The precise nature and source of Graves's feminist identification is not clear. Nonetheless, "feminism" enabled Graves to place her multifaceted critique within a systematic critical perspective. This systematic critical approach

makes salient the persistent gendering of biological phenomena and the valuing of male over female processes in the *SRY* model of sex determination, revealing gender as a factor in both the construction of the model and its widespread appeal despite its inadequacies. A "feminist view," as Graves describes it, placed a diverse set of critical insights that had motivated Graves's approach to sex chromosome and sex determination research for at least a decade into an easy-to-grasp organizing framework. Graves's "feminist view," then, is effectively presented as a relevant, well-motivated, and insightful critical perspective from which sex determination researchers might evaluate scientific models, identify potential sources of bias, and generate alternative hypotheses. Among several channels carrying feminist or gender-critical sensibilities into sex determination genetics in the late 1990s, Graves became among the most forceful, direct, and prominent.

The Normalization of Gender Criticism

Beginning around 2000, a marked shift of tone occurs in the sex determination genetics literature. As the *SRY* master gene model fell out of favor, questions and ideas once at the periphery flooded in from all sides, including gender-critical approaches. The shift was informal and not self-consciously feminist. Rather, a general awareness matured—not evident previously—of the pitfalls of androcentric and gender-dualistic thinking. Researchers took up and absorbed valuable feminist insights, often without realizing that they had done so. This gender-critical consciousness began to be engaged as a matter of course in the intellectual work of the field. I call this the normalization of gender criticism—one model of how feminist critical perspectives might find reception and take root in a scientific field.

The growth and effects of gender criticism are abundantly evident in the set of research questions that have come to occupy the field, changes to the model of sex determination itself, and the framework used by contemporary sex determination geneticists in explaining their research and describing the contribution of their work to biology and to society at large. Whereas "gender-critical" approaches are absent from the sex determination literature in the 1990s, in 2005, Fausto-Sterling's 1989 critique of sex determination models is echoed by prominent researchers in the mainstream literature of the field (though Fausto-Sterling is never cited). Researchers acknowledge neglect of research on the biology of female sex determination as a weakness in scientific

theories of sexual development and sexual difference. In addition, researchers seek to avoid language implying that male biological processes are active and dominant while female processes are passive and default. When using the concepts of "sex" and "gender," researchers take pains to resist the implication that biological sex maps plainly to social conceptions of sex and gender. Sex determination literature emphasizes a plurality of sexual phenotypes and multiple pathways to normal sexual development. In a variety of ways, in their scholarship, public commentary, and pedagogy, sex determination researchers signal their awareness of feminist critiques of the *SRY* model of sex determination and their sensitivity to the social consequences of scientific theories of sex and gender difference.

Two sources, transcripts of the 2001 Novartis Foundation symposium, "The Genetics and Biology of Sex Determination" (Novartis Foundation 2002), and a set of interviews of prominent sex determination geneticists commissioned by the Annenberg Foundation for an online biology education project in 2004 (Annenberg Foundation and Oregon Public Broadcasting 2004), provide a remarkable record of the normalization of gender criticism in this field.

Three themes are noteworthy in the 2001 discussions at the Novartis conference: (1) a new, broad consensus on the importance of research on ovarian determination to any sound model of sex determination; (2) the replacement of the "master gene" conception of *SRY* by a multifactorial model of sex determination; and (3) the call for a human-specific model of sex determination, acknowledging the distinctiveness and complexity of sex-gender systems from species to species and the special sensitivities required for research on the biology of human sex and gender (Novartis Foundation 2002).

Whereas the research gap on ovarian determination is mentioned as an aside in scattered literature in the 1990s, in 2001 it is repeatedly and urgently raised in papers and discussions. Lovell-Badge and coauthors write (all quotes from Novartis Foundation 2002):

> Considerable progress has been made over the last 11 years, such that it is now possible at least to formulate models of how sex determination may work in mammals. . . . However, we are no doubt still missing many relevant genes, in particular for the female pathway, both those that can be considered antitestis genes and those that are actively required for the specification of the cell types characteristic of the ovary. (15)

In a closing discussion about future priorities of the field, Koopman names ovarian development as a pressing problem for the field, acknowledging the gap in knowledge produced by the prior totalizing emphasis on the testis:

> In the coming decade, we are likely to see further progress in understanding one of the great black boxes in developmental biology, namely the molecular genetics and cell biology of ovarian development. Efforts to illuminate ovarian development have been overshadowed to some extent by progress in studying testis determination and differentiation. (247)

Male gonad formation was once the primary explanandum and "holy grail" of sex determination research. By 2001 a definitive shift had occurred. The research program was reconceived as identifying the multitude of factors involved in gonad differentiation from a bipotential state. In the transcribed conference discussion, for example, Eric Vilain, now a clinical geneticist at UCLA, prompts researchers to keep in mind that "pro-male" factors are only one research target (47, 49). "Pro-ovary" and "anti-testis" factors (which, importantly, may be distinct) await characterization; without these elements, Vilain argues, the genetics of sex determination remains poorly understood. This perspective, reiterated throughout the conference proceedings by Koopman, Graves, Lovell-Badge, and Francis Poulat (Institute of Human Genetics, France), among others, reveals a widely shared conceptual transformation of the research problem of sex determination.

Consistent with this, the Novartis transcripts also evidence a much-revised estimate of the importance of the *SRY* gene in sex determination. The field's earlier attachment to an all-powerful master "maleness" gene model now appears as a clear blind spot in previous thinking. One (anonymous) discussant points out that the problem with the model now appears obvious in light of empirical counterevidence and basic principles of evolutionary theory, and wonders aloud why Graves's intervention was necessary to make researchers aware of the oversight:

> For model systems where there are genetic tests, we often isolate and identify particular genes, and assign them certain roles. We then tend to think, "Ah, this gene must perform this function in a large number of organisms." . . . We are terribly surprised when we get results such as Jennifer Graves' demonstration that *SRY* is not the be-all and end-all of sex determination, when in fact this is probably a common theme in evolution. (99)

Goodfellow, who in 1992 claimed that the *SRY* gene contained "all of the genetic information that you need to make a male," in 2001 states that it is likely that *SRY* must interact with another gene, and that this interaction itself requires the assistance of cofactors:

> I guess what I am saying is that we have ignored the cofactor molecules . . . for too long. This is why I was emphasizing the possibility that we may be looking at soaking up a cofactor that is needed for the expression of another gene. (40)

In 2001, researchers assign the *SRY* gene a far more modest role in sex determination. Poulat characterizes *SRY* as an interchangeable regulatory element: "We say that *SRY* is only a box. We can exchange this box with other boxes. . . . Basically we have a truncated SOX9 protein, which is also more-or-less a box: nevertheless, in this case we have sex reversal" (36). Similarly, Lovell-Badge et al. describe *SRY* as "acting solely as an architectural factor" (12). Reflecting both the shift to a nonbinary, multifactorial model of sex determination that includes both male and female gonad determination and the trend in biology toward complex regulatory network models of gene action, the language of "master genes" is absent.

Finally, the 2001 conference discussants are newly and keenly aware of the specificities of *human* sex determination genetics. Early enthusiasts championed *SRY* as a tool for Olympic gender verification and the determinant of "what makes a man a man." In 2001, researchers are far more cautious. For example, Vilain reminds colleagues that "a majority of patients with abnormal gonad development remain unexplained genetically" (51). The failure of the *SRY* model to fully explain human sex determination, researchers acknowledge, arises in part from a too-simple binary conception of sex difference and in part from inconsistencies between mouse models and humans. Glossing over discrepancies, at first researchers held to a theory of sex determination as a fundamental and therefore well-conserved mammalian developmental pathway, validating the generalizability of the mouse model system for sex determination research. Researchers in 2001, confronting the breakdown of this model, are more attuned both to distinctions between mouse and human systems of sex and gender determination and to the particular dangers of transferring folk conceptions of sex difference as a simple binary to biological theories of sex determination. In 2001, we see human sex determination genetics developing into a distinct field of expertise and specialists urging colleagues to be mindful of the specificities of the human sex phenotype. Vilain,

for example, calls for a model of human sex determination that accommodates an "understanding [of] the tremendous phenotypic variability. . . . We often underestimate all manner of influences, from environment to genetic background" (253). Short adds, "we mustn't be sucked into thinking that [human] sex determination begins and ends with the gonads" (253).

The transcript demonstrates that this new gender criticality is directly linked to increased awareness among researchers of social and political issues raised by the intersex community. Responding to patient advocates, researchers work to challenge their own assumptions about "normal" sex phenotypes and the naturalness and necessity of a male-female sex binary. They appreciate the need for care and precision in research design and language use in sex determination research. For example, in a transcribed discussion (Novartis Foundation 2001) about recent research in human sex determination genetics, Goodfellow says:

> The dialogue that occurs between the medical profession and patient groups is something that the medical profession has to listen to. Not just with respect to this very difficult area, but generally. Treatment can reflect the social prejudices of the treaters. When a particular treatment is chosen because of the prejudices of the people who are performing that treatment, there has to be a social dialogue. The responsibility for the treatment of patients in the UK has changed in my lifetime. . . . Clearly, there is no easy solution to this problem, because unless social attitudes change dramatically we are dealing with individuals who fall outside social norms. . . . [W]e would be wrong not to engage in dialogue with those to be treated. (55)

Goodfellow's alarm about the potential for "prejudices" to influence scientific practice, his sense of responsibility to the intersex community, his awareness of the power and contingency of social norms about gender, and the easy interjection of these issues into a theoretical discussion of sex determination models, demonstrates the cross-talk between the conception of gender as a spectrum advanced by the intersex community and the cognitive work of the field of sex determination research.

Interviews conducted by the Annenberg Foundation in 2004 with leading sex determination geneticists Holly Ingraham, David Page, and Eric Vilain offer a second source documenting the normalization of gender-critical approaches in the field of sex determination research. The interviews echo and elaborate themes of the 2001 Novartis conference, while also presenting a more

fine-grained picture of the integration of gender criticism into the models and epistemic practices of the field. These sustained, first-person narratives reveal researchers' own evolving conceptions of sex determination and provide evidence of the broader intellectual framework in which these changes are understood by specialists.

The interviews demonstrate that today's sexuality spectrum, gene dosage model of sex determination is broadly undergirded by a gender-critical conception of human sex and gender. Researchers explicitly link the new model to the development of a changed, more complex understanding of gender in the field, and the old to a set of biased assumptions about the biology of sex. Vilain, for instance, describes the 1980s and 1990s conception of sex determination as "a simplistic mechanism by which you have pro-male genes going all the way to make a male" (Annenberg Foundation and Oregon Public Broadcasting 2004). The model assumed that the male-determining gene contained all that was necessary, Page says, to "impose" masculinization on a bipotential gonad. Page describes this model as "extraordinarily male-biased"; "extremely biased in favor of the male"; "the most obvious hole in our understanding of the development of anatomic differences."

Ingraham, Vilain, and Page all narrate the history of the master gene *SRY* model of sex determination as a lesson in the dangers of building unreflective assumptions about gender into scientific theories. As Page relates, "Biologists have been saying for half a century that female development is a default outcome that somehow all human or mammalian embryos are initially female and then have masculinity imposed on them. I don't think that the available data supports this idea." Vilain explains, "We used to think that females were the result of a default passive sex-determining pathway and we now know that is not true." Ingraham further suggests that the old model reflects biased interests of male researchers, less invested in characterizing "the active processes in females." She discloses, "I wish I could understand it because I am female and I would like to know why I'm female and what are the active components to my gender assignment."

When describing today's model, the researchers emphasize the inclusion of female developmental processes and a dynamic and nonbinary understanding of sex. For example, Vilain says:

> We [are] entering this new era in molecular biology of sex determination where it's a more subtle dosage of genes, some pro-males, some pro-females, some anti-males, some anti-females that all interplay with each other rather than a simply linear pathway of genes going one after the other.

Similarly, Page says:

> Both the male and female pathway are very active and require highly orchestrated, highly integrated sets of events, extremely complicated biochemical cascades that we're only beginning to understand.

In these descriptions of the genetic model of sex determination, the researchers' emphasis on the complexity of sex determination, the activeness of both male and female processes, the parity of male and female genetic contributions to sex determination, and the interaction of male and female factors all reflect a deeper shift toward a gender-critical understanding of sex and gender. Vilain says, "there [are] many ways to define sex and each one of them [is] just as equally important as the other." Page says, "[O]ften we fall all over ourselves because of the limitations of the definitions we try to impose" on sex. He adds, "There is no such thing as a simple definition [of gender] and even within a scientific context, sex or gender has been defined at many different levels." Ingraham highlights the diversity of human gender identities, arguing that mouse studies imposed an idealized conception of gender on the research problem and that human sex determination must be contextualized in the phenotypic variability of sexual identity. "[H]ow are you going to find a transsexual mouse? Are you going to ask him [sic]?"

Today gender criticism is part of specialist discourse in the field of sex determination research in a way that it was not in the 1980s and 1990s. As Sinclair, who discovered *SRY* in 1990, said in an interview: "I think humans like things to be ordered, and they get bothered about gray areas and when things become less clear-cut. But these days I don't think so much in black and white about male and female. Now I think of it all as being on a spectrum" (Beale 2001).

It is possible to explicitly link this gender-critical perspective to the cognitive content of sex determination research. Here we have observed gender criticism come to play a part in the larger organizing conception that researchers use to think about sex determination, the descriptive language of sex determination, and the day-to-day work of evaluating hypotheses and interpreting data. In their own words (even if often painfully unaware of the contributions of feminism to their work), we see that researchers have found gender criticism valuable to their thinking, and we can observe gender analysis entering into the standard epistemic strategies for criticism and analysis in this field.

This chapter profiles the social and epistemological advancement of gender criticism in the field of sex determination research during the 1990s. My focus on the gender dimension of sex determination research is, needless to

say, not meant to imply that beliefs about gender were the *sole* factor shaping the *SRY* model of sex determination, nor that gender criticism was the sole motive force in the development of a new model. Gender criticism interacted with other factors, including advances in technology, new gene discoveries, and a broader rethinking of "master gene" theories in developmental biology over the past twenty-five years. Nonetheless, the contribution of gender criticism has been significant.

Notes to Chapter 2

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1. The term *mainstreaming* is often used to describe the integration of feminist ideas and methods into the dominant practices of a field, but in this instance the term *normalization* is more appropriate. The field of sex determination genetics experienced a quiet and mostly unacknowledged shift in its epistemic practices. The term *normalization* is intended to highlight this feature of the entry of gender criticism into the field. In contrast, *mainstreaming* generally refers to explicit changes in social and institutional practices in which gender is systematically recognized as a category of analysis, as in changes to hiring and diversity practices, curricula, or the kind of scholarship recognized as prestigious in a field.

2. A further reason for the early and intense interest in the male sex-determining gene may be the dominance of the field by male researchers. This may have influenced both the research agendas and the culture of research and discovery. Bryan Sykes, for example, portrays the search for the male sex determining gene in the late 1980s as a "hunt" and a "race," a "spectator sport where the prize for winning was the glory of being first." Sykes also notes that David Page named his proposed sex-determining gene "DP1007"; writes Sykes, "I am sure I am not alone in noticing the initials and a certain masculine resonance in the last three digits" (2003, 60–66).

3. Graves's Y chromosome degeneration hypothesis, which predicts the disappearance of the mammalian Y chromosome over the next ten million years (Graves 2006), has become a curious flashpoint for cultural anxieties around feminism and male social status. Steve Jones's *Y: The Descent of Men* (2002) and Bryan Sykes's *Adam's Curse* (2003), which symbolically link the degeneration of the Y chromosome to the decline of male social status in the face of feminism, are representative.