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2003 CURT STERN AWARD ADDRESS
Introductory Speech for David Page*

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I am pleased and honored to be able to introduce David Page, this year's winner of the Curt Stern Award.

To give this award to David in 2003 seems highly appropriate, because this year marked the seminal achievement in his quest to define and understand the human Y chromosome, its evolutionary history, its genetic and genomic content, and its relevance to the biology and health of half of our species.

David burst onto the scene of human genetics while still a medical student at Harvard in the early 1980s. It was there that David developed his keen appreciation for the value of genetic variants to understand the biology of an organism. It was David Botstein, David Page's research mentor at the time, who coined the oft-quoted phrase about "the awesome power of yeast genetics." If it was David Botstein who led much of the explosion in the use of experimental mutations for genetic analysis in yeast, it has been David Page who has been so determined—and so successful—in exploiting "the awesome power of human genetics," using naturally occurring variants to reveal so much about human biology and medicine.

After his training at Harvard and MIT, David Page became a fellow at the Whitehead Institute, from 1984 to 1988, and subsequently joined the faculty at the Whitehead and in the Department of Biology at MIT, in 1988. He was appointed to the Howard Hughes Medical Institute in 1990 and is now professor of Biology at MIT, associate director of the Whitehead Institute, and a full investigator of the Howard Hughes Medical Institute.

David's record of accomplishment reads like a "top 10" list of major achievements in understanding the biology of mammalian sex chromosomes:

- he first proved the concept of homologous sequences on the X and Y chromosomes;
- he defined and then proved (with his longtime collaborator, Albert de la Chapelle) the concept of X-Y interchange as an explanation for human XX males;
- in a series of key papers published over the past 20 years, he reconstructed the evolutionary history of our sex chromosomes from an ancestral pair of autosomes some 300 million years ago;
- he and his group developed the first detailed deletion and contig map of any human chromosome;
- he uncovered the unique functional coherence of genes on the Y chromosome, which, rather than being expressed in a range of different tissues (as are, for example, genes on autosomes or the X chromosome), are to an unprecedented degree expressed in only a single tissue lineage, the germ line;
- he defined the major Y-chromosome deletion that accounts for a high proportion of cases of male infertility and continues to explore the role of the Y in influencing fertility;
- and, finally, earlier this year, he reported the nearly complete sequence of the human Y chromosome and uncovered an unanticipated high level of sequence conversion between the two halves of large palindromes that dominate the genomic landscape of the Y.

When thinking of David's work, three characteristics come to mind. First, he has been fiercely thorough and focused in using patient material to reveal substantial insights into sex-chromosome biology. He recognized, years ago, the value of collecting large numbers of patient samples with sex-chromosome defects, an approach that has turned out to be even more valuable over time, as an increasing number of genomic resources have become available. Without his insights, it is unlikely that we would understand nearly as much as we do about X- and Y-chromosome defects, their origins, and their medical consequences. Second, he has been fearless in putting forward often-controversial notions, recognizing (correctly, in my view) that the value of an hypothesis lies less in whether you are right or wrong than in providing both a framework and a motivation to test various predictions of the hypothesis. Third, David has been doggedly comprehensive in his pursuit of the questions he is most passionate about. He deserves much credit for his thoroughness in guiding the line of experiments he and his colleagues and

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students have conducted. His curriculum vitae contains ample evidence of this; there are very few "off track" papers and even fewer unfinished stories. His papers are masterful explorations, comprehensive not only in the data but in the detailed evaluations of the implications—genetic, genomic, medical, mechanistic, diagnostic, evolutionary—of the work. I can think of very few in our field whose written contributions have been put together with the clarity and depth of scholarly reflection of those from the Page lab. His dedication to effective communication carries over to the spoken word as well. Simply put, I cannot think of anyone who is more capable of telling a good story. He is exceptional in organizing his thoughts and data and in conveying to his audiences the sense of passion, commitment, and deep understanding that he brings to his work.

Ironically, but most appropriately, it was Curt Stern himself who first brought aspects of Y-chromosome biology and inheritance to the attention of members of this Society. In April 1957, during his year as president of the Society, Stern gave his presidential address on the topic of Y linkage, with the subtitle "On the Alleged Sins of the Y Chromosome." At the time of that address, the role of the Y in mammalian sex determination and male fertility was still unknown, and details of the gene repertoire and genomic complexities of this chromosome were hardly dreamed of. At the time of that address, David Page was all of 9 months of age, growing up in Harrisburg, Pennsylvania.

We have come a long way in learning about the Y chromosome since 1957. If it was Stern who first told us about the "sins" of the Y chromosome, it has been David Page who has led the chromosome to its ultimate genetic and genomic salvation.

I am pleased to introduce David this afternoon and to present him with our Society's 2003 Curt Stern Award.