Rise and Fall of the Y Chromosome

Biologists are coupling theory and experiment to explain why—in species after species—the sex-determining chromosome loses most of its active genes

Call it "physics envy." That's the term used by some evolutionary geneticists to describe their discipline's quest to unveil incontrovertible laws governing the evolution of organisms, just as physicists derive general principles to explain how matter works. Envy arises because the search has proved to be so difficult. In fact, aside from the basic principle of natural selection, exceptions to biological rules invariably turn up. Still geneticists haven't given up hope, and there are now signs this persistence may be rewarded in at least one area: the evolution of sex chromosomes.

Many animals with disparate evolutionary lineages—mammals and birds, as well as certain species of fish, reptiles, and insects—have independently developed distinct sex chromosomes, which are often designated X and Y. In mammals, they make males, since females have two Xs; in birds it is the females that are XY. Biologists suspect there must be a powerful evolutionary force pushing all these species to come up with the same evolutionary solution. It also appears this same force is driving the Y chromosome to extinction. Virtually identical in their earliest evolved stages, the X and Y become increasingly dissimilar until, in many species, the Y is a shrunken shadow of its partner, carrying a paltry complement of active genes. "It's a pattern you see over and over, and it's always been a puzzler: Why the hell does the [Y] chromosome end up as a little blob with hardly any genetic activity on it?" asks Jim Bull, an evolutionary geneticist at the University of Texas in Austin.

A new experiment may hold the answer to Bull's question—as well as the germ of a general principle that governs the evolution of the Y. The principle takes hold during meiosis, the process that creates the eggs and sperm. Rather than recombining genetic material at this stage, as other chromosomes do, the most dissimilar Xs and Ys—such as those in humans—exchange barely any information at all.

On p. 230 of this issue, William R. Rice, a population geneticist at the University of California, Santa Cruz, reports that a lack of recombination is the key to the Y chromosome's undoing. Rice engineered a genetically active fruit fly Y chromosome but prevented it from recombining with the X. After many generations, the Y began to deteriorate, losing active genes. "There've been several different theories about why this odd chromosome ends up degenerate," Bull explains. "What Rice has done is to start laying an experimental foundation for some of these theories."

These latest results are the fruits of a long search. As early as the beginning of this century, researchers observed that Y chromosomes travel along an evolutionary pathway in several groups of animals. Take fish. Some species have virtually identical X and Y chromosomes, with the exception of a sex determining locus on one chromosome. This is presumably the original, most primitive arrangement, in which a lot of genetic material is exchanged between the X and Y during meiosis. Other fish species have Xs and Ys that are very different and have largely stopped recombining. Finally, some have no Y chromosomes at all.

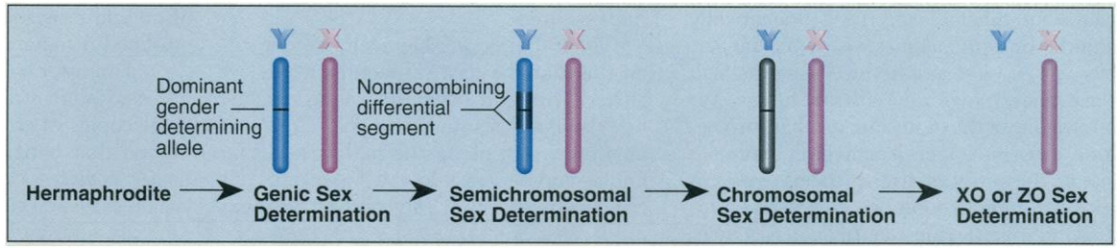
"The first thing to explain in this progression," Rice says, "is why do the X and Y stop recombining?" In 1931, the late geneticist Sir Ronald A. Fisher proposed that an accumulation of sexually antagonistic (SA) genes (alleles beneficial to one sex but harmful to the other) triggered this development. For instance, Rice notes that in several fish species, such as the guppy, males have evolved a bright red spot (due to a Y-linked allele) because females prefer gaudy mates. But such ornamentation carries a price: Predators easily spot the males. Yet the males persist in their colorful displays, presumably because the mating benefits outweigh the predatory costs. For females, however, there is nothing to be gained by donning flashy colors except a chance to become a meal; they lack the gene.

Biologists believe that when the gaudy gene first appeared, it was in females as well as males, leaving females with a predator problem. "Over evolutionary time, there has to be some way to resolve this antagonism," says Rice, "and one way is to break down the recombination between the X and the Y." As a result of this segregation, the gaudy color gene would still be passed along—but only from fathers to sons.

In a similar manner, other SA genes beneficial to males and occurring near the male-determining gene should increase in number. As they do, increasing portions of the X and Y will stop recombining. "Theoretically, this piecemeal process should continue until the entire chromosome is locked up, preventing the X and Y from recombining over their entire length," explains Rice.

Fisher's idea was interesting, but far from satisfying the rigor demanded by physics envy until 2 years ago, when Rice demonstrated experimentally that a sex-determining gene in fruit flies acts as a "hot spot" for accumulating SA genes—thus setting in motion a mechanism to halt the recombination of the X and Y chromosomes (*Science*, 5 June 1992, p. 1436).

But why would the end of a trading relationship lead to the diminution of the Y? Again, theorists have had some ideas, one of the most recent coming from Brian Charlesworth, an evolutionary geneticist at the University of Chicago. In 1978, Charlesworth argued that an evolutionary mechanism known as "Muller's ratchet" (after the geneticist H. J. Muller, who proposed it in 1964) could explain the degeneration. As originally conceived, the theory held that without recombination, errors would continually accumulate in a finite population through chance, by the random loss of the



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Y evolve? In theory, the nonrecombining segment of the Y chromosome expanded as animals moved from a hermaphroditic state to chromosomal sex determination; eventually, the Y's inability to recombine causes it to disappear.

least mutated genome. And like a ratchet wheel that only moves in one direction, this process can never be reversed: Once mutants replace healthy genes, the good genes don't come back without recombination to replace them, while other bad genes continue to accumulate. Charlesworth hypothesized that a similar ratcheting effect could operate on a nonrecombining Y chromosome, given a sufficiently high mutation rate in a finite population over hundreds and thousands of years.

Rice verified this by speeding up time. He made two chromosomes in a line of fruit flies (*Drosophila melanogaster*) behave as if they were one large Y, and he kept the population size small. These "microevolutionary tricks," as he calls them, together sped up the rate of decay. "The bigger the Y, the more chances there are for errors to occur," Rice explains, and in a small population, the errors would spread rapidly. He ran five 35-generation experiments, and in all five found the Y degenerated. This accounts for the functional losses, although there's uncertainty about the mechanisms behind actual physical shrinkage. Once a gene doesn't work anymore, Rice suggests, there's no selective pressure to maintain it, and physical deletions can occur.

But was Muller's ratchet the reason that big Ys accumulated the deleterious genes? Rice argues that it was, and Charlesworth agrees—with one caveat. "Muller's ratchet is probably going on [in Rice's experiment]," he says, "but there is no way to sort out how much of the decline is due to it and how much is because of chance fixation." Fixation refers to genetic mistakes that accumulate because of random genetic drift, a process which occurs in both sexual and asexual populations; Muller's ratchet operates only in asexual populations. "Still, the implication of his experiment suggests that the parameters required for Muller's ratchet to work do come within the ball park even in a very large population," Charlesworth says.

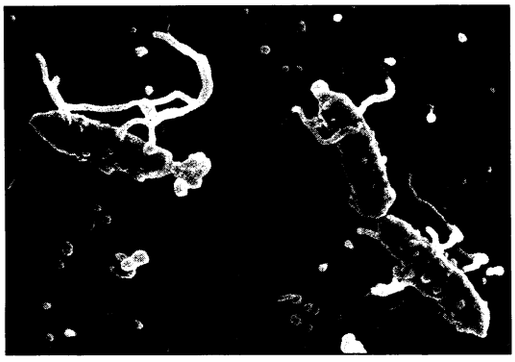
Evolutionary geneticists now hope that Rice's work, coupled with Charlesworth's hypotheses, may one day add up to a universal evolutionary law. "It might be something on the order of: 'Once a Y chromosome stops recombining it is doomed to lose all, or virtually all, of its genetic activity,'" suggests Rice. Eventually, the law might even be extended to asexual species, since there is a curious parallel pattern. "What intrigues me about this phenomenon of the Y not recombining and degenerating is how closely it mirrors what happens to asexual species," Rice says. "We know that most asexual species are at the tips of the tree of life; that they are doomed to extinction, apparently because of the lack of genetic recombination. It may be that the same mechanism that causes the Y to degenerate also causes asexual species to die out." Researchers consumed by physics envy might even consider expressing that in terms of an equation.

–Virginia Morell

INFECTIOUS DISEASES

Unveiling a Tuberculosis Drug Target

When an age-old scourge learns some new tricks, the results can be deadly. And the plague of tuberculosis, rising dramatically around the world, comes with some dangerous new ploys: strains of the disease that can resist many previously effective drugs. Yet knowledge of the molecular mechanisms behind drug resistance is emerging almost as fast as the resistant strains themselves. On page 227, a collaboration of U.S. and New Zealand investigators identify a new gene in *Mycobacterium tuberculosis*, the TB agent, that is implicated in resistance to isoniazid, one of the most popular anti-TB drugs.



W. JACOBS

Bugs say no to drugs. A mutation in one gene can make mycobacteria resist tuberculosis drugs.

This gene, they suspect, makes the protein that is the drug's primary target; when the gene is overexpressed or mutated, it frustrates isoniazid's effectiveness. Collaring it should allow scientists to develop quicker ways of identifying TB patients who carry isoniazid-resistant strains. Perhaps even more important, the discovery promises to aid the search for isoniazid-analogs that sidestep resistance.

Given that potential payoff, it's not surprising that the medical community is excited. "They still haven't answered exactly how isoniazid resistance works, but it's an important step along the pathway to that understanding," says Joseph Bates, a bacterial geneticist at the University of Arkansas in Little Rock.

Isoniazid has been in use against tuberculosis since 1952, but investigators have never quite understood how it works. Excitement mounted in 1992 when a group reported in *Nature* that the deletion of a different gene—one that codes for an enzyme called catalase—conferred resistance on some strains of the TB microbe (*Science*, 21 August 1992, p. 1038). But the discovery didn't solve the mystery of isoniazid's action; researchers believe the enzyme merely concentrates or activates the drug inside the bacteria. The best hypothesis on isoniazid comes from indirect evidence indicating the drug blocks synthesis of mycolic acid, a fatty acid that's part of the cell wall of all mycobacteria.

Investigators now believe they have the genetic smoking gun to back up these biochemical clues: The new suspect gene codes for a protein that probably plays a role in mycolic acid synthesis. The U.S.-New Zealand research group, led by William Jacobs, a Howard Hughes investigator at Albert Einstein College of Medicine, came across it while analyzing the genomes of two species of mycobacterium, related to but faster-growing than the slow-growing TB organism, and thus easier to study. From some isoniazid-resistant microbes, investigators isolated a mutated fragment of DNA that could transform normal mycobacteria into drug-resistant strains. After examining normal copies of that fragment, Jacobs' team found that it held a specific gene, labeled *inhA*, coding for a protein that strongly resembles several bacterial proteins implicated in fatty acid synthesis.

Jacob's group and others are now analyzing TB bacteria from patients harboring isoniazid-resistant strains and have found *inhA* mutations in many of them. If alterations in *inhA* and the catalase gene do account for the large majority of drug-resistant strains that turn up in patients, and ongoing studies may determine that within the year, physicians could use a DNA-based diagnostic test to find out quickly whether a patient is infected by isoniazid-resistant microbes and alter treatment accordingly.

The gene will also give a boost to drug development against all mycobacterial infections. Investigators hope to create a new generation of more effective isoniazid-like drugs that disrupt the construction of mycolic acids. "What's required now is a concerted effort to understand the biosynthesis of mycolic acids," says Colorado State University microbiologist Patrick Brennan. "[This discovery] gives us the academic background for an onslaught of new chemotherapies." And as the incidence of drug-resistant strains of TB rises, those weapons are desperately needed.

–John Travis