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## New Evidence Pushes Back Age of Sex-Determining Chromosomes

Comparison of genes on the sex-determining X and Y chromosomes indicates that the ancestor of human sex chromosomes first arose from an identical pair of standard chromosomes approximately 240 to 320 million years ago, shortly after the divergence of the evolutionary lines leading to mammals and birds.

"The first events that created the sex chromosomes had been thought to have occurred at least 170 million years ago," said [David Page](#) of the Howard Hughes Medical Institute (HHMI) at the Whitehead Institute for Biomedical Research. "We're pushing that back another 100 million years or so."

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- **David C. Page**

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Chromosomes of animals and plants generally occur in matched pairs. In humans, women have two X chromosomes and men have an X and a Y chromosome. During meiosis the process that generates sperm and egg cells partner chromosomes exchange pieces of DNA. But in many species, mammals included, the X and Y chromosomes are a mismatched pair that for the most part does not exchange genetic material. The exception to the rule is that the tips of the X and Y chromosomes recombine during male meiosis in humans.

Page's and Bruce Lahn's analysis of the sex-determining chromosomes, which was published in the October 29, 1999, issue of the journal *Science*, reveals that four major genetic shuffling events were responsible for the generation of distinct X and Y chromosomes. Each of these events caused an inversion and shuffling of regions of DNA on the Y chromosome so that they could no longer line up with analogous regions of DNA on the X chromosome partner. This prevented DNA exchange between the similar regions of the two sex chromosomes, and made it possible for portions of the X and Y chromosomes to differentiate from each other.

Once X-Y exchange was curtailed, these regions of the X and Y diverged through the accumulation of occasional mutations on one chromosome or the other. Some of these gene mutations were evolutionarily "silent" meaning they had no effect on the functioning of the genes. Natural selection should not alter the rate at which these silent changes accumulated, so Page was able to count the number of random mutations and use that information as a sort of molecular clock by which to measure evolutionary time. Page and his colleagues reasoned that the greater the number of mutations, the longer the two genes must have been isolated from each other and prevented from intermixing.

"Before these shutdowns of recombinations, genes on the X and Y were like water that's dammed up," said Page. "But there have been four times in the history of the mammalian sex chromosomes over the last 300 million years when the dam was opened and a bunch of genes flowed down the evolutionary stream. Since these dam openings were so widely separated in time, the groups of genes have gone different distances down stream."

Using genetic sequence information obtained from a variety of sources, Page identified nineteen genes that have similar copies on both the X and Y chromosomes, and he measured the number of silent mutations that each pair of genes contained.

He found that the gene pairs fell into four groups or "strata." Each of the four groups was distinct as measured by gene sequence similarity and by geographic position on the chromosomes. The X chromosome members of the most dissimilar and therefore oldest pairs of genes were at one end of the chromosome, and those from the most similar, or youngest, pairs were at the other end, with two intermediate groups in the middle.

"We didn't anticipate that the numbers just fell out," said Page. "It's stunningly beautiful."

DNA rearrangement events are rare and irreversible. If two species of animal show evidence of the same genetic rearrangement, the original event almost certainly occurred in a common ancestor. Page used similar logic to estimate that the first of the four rearrangement events occurred in the X and Y chromosomes sometime between 240 and 320 millions years ago. Previous estimates had placed the origins of the X and Y chromosomes at roughly 170 million years ago, said Page.

Based on this and earlier work by other groups, Page believes there is a set pathway for creating a pair of sex chromosomes. In some species, sex can be determined with no genetic differences in chromosomes. In crocodiles and turtles, for example, the temperature at which an egg is incubated determines the animal's sex. But at some point, a random mutation on a non-sex chromosome, known as an autosome, may favor the development of one sex over another. In mammals, that defining event was probably the alteration of an existing gene to create the male-promoting *SRY* gene on the Y chromosome.

"That's the evolutionary equivalent of a hijacking," said Page. "That pair of autosomes, previously with no male or female leanings, is then taken inexorably down the path that we describe."

The next step on the road to the development of sex-determining chromosomes is a rearrangement on the Y chromosome. Natural selection favors this event because the rearrangement prevents part of the Y chromosome from lining up with the X. This, in turn, keeps the mutated male-favoring gene, *SRY*, from mixing with the female-favoring or neutral version on the X chromosome.

In the case of the human sex chromosomes, other male-favoring and male-specific genes eventually found their way to the Y chromosome so that they could be passed along to subsequent generations along with *SRY*, Page says. Further rearrangements in the regions containing these genes spread along the Y chromosome, resulting in conditions that made it much less likely that male-specific genes could mix with genes on the X chromosome.

The most famous example of such gene clustering is in fish. Male guppies have a number of genes for making flashy fins to attract females, and those genes are clustered on the male sex chromosome. The downside is that the flashiness may also attract predators. The female guppy wants to avoid predators, so she wants no color. "But for the male," said Page, "it's a net

benefit if he can raise his chances of mating before he's eaten."

The flip side of this process is the disposal of unwanted or unneeded genes on the Y chromosome. Genes that are not needed by the male may gradually accumulate problematic mutations. In the female, a mutated gene on one X chromosome can be compensated for by a "healthy" gene on the other X chromosome. In the male, however, there is no such shuffling between X and Y, so the unneeded genes on the Y tend to become useless and are eventually sloughed off. The result is a shrinking Y chromosome that has fewer and fewer genes in common with the X.

This explains why most of the X-Y gene pairs identified by Page are in the younger regions of the X chromosome. Most of the Y versions in the older regions have already been lost. In the younger regions, the process of loss will continue. "In humans," said Page, "the ramifications of the hijacking are still being played out."