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## Mutation Rate of Male Sex Chromosome Lower than Expected

Genetic sequencing and analysis of regions of the X and Y chromosomes of humans, chimpanzees and gorillas, reveals a much smaller difference in mutation rates of the two sex-determining chromosomes, say researchers from the Howard Hughes Medical Institute at the Massachusetts Institute of Technology.

The results cast doubt on the idea that sperm production is inherently more prone to error than egg production. The finding also means that genetic-disease-producing mutations that had been attributed to what was thought to be a fundamentally higher mutation rate in males must now be explored in terms of their individual underlying causes, says HHMI investigator David C. Page, who is at the Whitehead Institute for Biomedical Research at MIT. Page and Whitehead colleagues Hacho B. Bohossian and Helen Skaletsky report their conclusions in the August 10, 2000, issue of *Nature*.

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"We were led to pursue this question because an understanding of how mutations arise is part of the fundamental underpinnings of human genetics," said Page. "Without mutations, there would be no genetic variation and, thus, no genetics. And this particular question of the balance of mutations that arise in mothers as compared to fathers has been a fundamental question in genetics for more than half a century."

Page and his colleagues set out to examine differences in mutation rate because they believed that previous measurements may have been skewed because the earlier studies were based on comparisons of corresponding genes on the X and Y chromosomes that may have been under different evolutionary constraints. Page's team chose to compare DNA sequences

within large regions of the human X and Y chromosomes that showed no evidence of harboring genes, and thus, would be far more likely to represent accurately the base mutation rate of those chromosomes.

The regions of X and Y studied by Page's team showed nearly 99 percent identity because these regions had undergone massive DNA sequence swapping between the two sex chromosomes only three to four million years ago, during the evolution of humans. To ascertain the original, primitive sequences of those regions, the scientists used homologous segments of the X chromosomes of chimpanzees and gorillas, which are more closely related to humans than species used in previous studies.

"Those earlier studies had looked at much older duplication events in primates, using sequences that were much more diverged from each other," said Page. "With regions containing 99 percent similarity, it was very easy for us to find those single nucleotide substitutions and to be sure that they represented isolated one-time events.

"It's like going out on a perfectly smooth beach early in the morning after the tide has gone out and counting raindrops on the unmarked surface. We were dealing with a very clean experiment of nature, in which every individual mutation was captured."

The scientists selected as a target for their study a portion of the highly homologous regions—composed of about 38,600 nucleotides—that was found in the human X and Y chromosomes and in the chimpanzee and gorilla X chromosomes. Their sequencing and comparison revealed that this segment of the human X and Y chromosomes differed in only 441 nucleotides.

The scientists then pinpointed the mutations in human sex chromosome by comparing each nucleotide variation with sequence data from the chimpanzee and gorilla X chromosome sequences. For example, if a particular nucleotide alteration was found on the human Y chromosome, but not on the human, chimpanzee or gorilla X chromosome, the mutation was presumed to have taken place on the human Y chromosome.

Using this technique, the scientists were able to infer which human sex chromosome originally harbored a given nucleotide substitution. From these data, they calculated a male-female mutation rate ratio of about 1.7—much lower than the previously suggested ratio of 5.

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The finding of such a modest difference in X and Y mutation rates could have important consequences for genetic studies of inherited diseases, said Page.

"Until now, the far greater number of cell divisions involved in making a sperm than in making an egg has provided a very attractive rationalization for what appeared to be the much higher mutation rate in the male versus female

germline," he said. "However, our results suggest that there is something closer to sexual parity in mutation rates." This parity implies that the cell divisions involved in making sperm are of much higher fidelity than was previously appreciated, said Page. Also, he said, the finding challenges scientists to explore differences among cell divisions in terms of mutation risk.

"Our findings have implications, not just for disorders that are sex-linked, but for all genetic disorders where mutations are a major contributor, regardless of chromosomal sites, and regardless of whether they affect boys or girls," Page emphasized.

The higher incidence of Y chromosome mutations that produce some inherited diseases could be due to specific, highly mutable nucleotide positions—mutational "hotspots"—that represent departures from the normal rate of mutational. Thus, understanding these anomalous mutation sites might require a better understanding of how the particular sequences might be prone to mutation said Page.

"We have now moved the baseline considerably, so that these hotspots now appear as very special cases, that really have to be studied and understood as special cases," he said.