WHITEHEAD INSTITUTE

MEN ARE NOT IN DRIVER'S SEAT OF HUMAN EVOLUTION

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CAMBRIDGE, Mass. — For more than half a century, the field of human genetics has harbored a gender bias about the relative contribution of males versus females to human evolution. Since 1947, when biologist J.B.S Haldane suggested that the rate of genetic mutation is much higher in the male germ line than in the female germ line, geneticists have credited males with much of the evolutionary changes that occurred in the 5 million years since human ancestors departed from chimpanzees.

But a new study comparing DNA sequences of the two sex chromosomes—the X and the Y—overturns this "male-driven" notion of human evolution and shows that males and females contributed fairly equally to the process. The study, published in the August 10 issue of Nature, was led by David Page of the Whitehead Institute and the Howard Hughes Medical Institute.

"This finding was totally unexpected and came as a big surprise to us. It flies in the face of the thinking that we've long held in human genetics that men are in the driver's seat when it comes to human evolution,"says David. The finding also has implications for medical genetics and helps answer one of the fundamental questions in human genetics: when a child is born with a genetic disease caused by a new mutation, what is the relative likelihood that the mutation arose from the mother or the father?

In some genetic diseases, such as hemophilia and dwarfism, where a substantial number of cases are represented by new mutations, a majority of the mutations do arise in the male germ line and seemed to support the notion of male-driven evolution. However, even though these diseases are male-driven, they are not the norm as previously thought but exceptions to the rule, says David who revisited this question as part of his bigger research project on sequencing the Y chromosome. Because the Y chromosome is a lone ranger in the genome world—unlike any other chromosome, it has no partner—its sequence is expected to contain certain unique traits not found in other chromosomes.

Over the past few years, the David lab has been conducting a "molecular" fossil dig, reconstructing the evolutionary history of the Y. His lab has already shown that the Y chromosome began its evolutionary odyssey as an autosome (a non-sex chromosome) that was then hijacked by male genes and has evolved over the last 300 million years into a haven for male fertility genes.

In this study, David and his colleagues compared a large chunk of DNA that is virtually identical on the X and the Y chromosomes. This identical region resulted from a genetic event 3 million years ago when the Y chromosome acquired a "Xerox" copy of a chunk of DNA from the X chromosome. This happened 1 to 2 million years after human ancestors departed from the ancestors of chimpanzees.

Today, that region is about 99 percent similar in the X and the Y, and the 1 percent difference in the DNA sequence reflects the new mutations acquired by the two chromosomes. This region therefore provides researchers an ideal way to estimate relative mutations in the X and the Y in human evolution.

In this study, scientists compared this region in the X and Y of humans and the X chromosomes of gorillas and chimpanzees.

When researchers calculated the ratio of mutation rates in males versus females, they found that it was 1.7—dramatically lower than previous estimates, which had suggested that the ratio was 5.

David says several factors account for this discrepancy, and posits that this study presents the most accurate figure. Previous studies compared divergence of genes on X chromosomes and Y chromosomes using widely different species of primates as the frame of reference for measuring the ratio. By contrast, the David lab study uses hominids as the frame of reference. Also, previous studies were based on analyses of genes on the X and the Y chromosomes, which are subject to selection bias. The David lab analysis purposely chose to analyze a region of junk DNA, a region that has no genes, so as to avoid selection bias.

"Understanding mutations is the bedrock of human genetics. It underlies human disease and human variation, without which there would be no evolution," says David.

"The Y chromosome represents a grand experiment of nature—a 300 million-year experiment with many subplots, and this is one of many," says David. When the entire sequence of the Y chromosome is deciphered later this year, the results will reveal many interesting pieces of information about gender differences in our species, he says.