Sex chromosome shocker: The 'female' X a key contributor to sperm production

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Painstaking new analysis of the genetic sequence of the X chromosome—long perceived as the "female" counterpart to the male-associated Y chromosome—reveals that large portions of the X have evolved to play a specialized role in sperm production.

This surprising finding, reported by Whitehead Institute scientists in a paper published online this week in the journal *Nature Genetics*, is paired with another unexpected outcome: despite its reputation as the most stable chromosome of the genome, the X has actually been undergoing relatively swift change. Taken together, these results suggest that it's time to reexamine the biological and medical importance of the X chromosome.

"We view this as the double life of the X chromosome," says Whitehead Institute Director David Page, whose lab conducted this latest research.

"The X is the most famous, most intensely studied chromosome in all of human genetics. And the story of the X has been the story of X-linked recessive diseases, such as color blindness, hemophilia, and Duchenne's muscular dystrophy," Page adds. "But there's another side to the X, a side that is rapidly evolving and seems to be attuned to the reproductive needs of males."

Page's lab, best known for its pioneering investigations of the Y chromosome, embarked on a rigorous comparison of the mouse and human X chromosomes, in part to test the longstanding biological tenet

that the gene content of X chromosomes is conserved and shared across mammals. However, to render such a comparison valid, the lab had to upgrade the human X reference sequence, which was originally assembled as a mosaic of sequences from the X chromosomes of at least 16 people. This composite left the reference with errors and gaps that fail to capture so-called ampliconic regions containing segments of nucleotides that are virtually identical. Such near-complete identity prevents recognition of tiny but important differences.

To set the sequence straight, the lab turned to the unique sequencing method Page had developed with collaborators at Washington University in St. Louis to help navigate the structural complexities of the Y chromosome. As Page reported roughly a decade ago, the Y contains several regions of large palindromes—areas of mirror-imaged genetic sequences. Such regions defy elucidation via conventional sequencing approaches, which simply cannot detect extremely subtle genetic differences found hidden among the "mirrors." In response, Page and colleagues devised what is known as SHIMS (single-haplotype iterative mapping and sequencing) to establish a definitive reference DNA sequence of the Y chromosome.

Using SHIMS, the lab greatly improved the human X reference sequence, accurately assembling three large amplicons, identifying previously unknown palindromes, and ultimately shortening the entire length of the sequence by eliminating four major gaps. These important updates will now be incorporated into the reference sequence of the human X for use by the greater scientific community.

Upgraded reference in hand, the lab discovered that, as might have been expected, the mouse and human X chromosomes have nearly 95% of their X-linked, single-copy genes in common. Almost all of these genes are expressed in both sexes. Strikingly, however, the lab identified approximately 340 genes that are not shared between the two species.

Fittingly, most of these genes reside in ampliconic regions of the X and appear to have been acquired independently during the 80 million years since mouse and human diverged from a common ancestor. Expression analyses revealed that these genes are active almost exclusively in testicular germ cells, where, at a minimum, they likely contribute to sperm production. Further exploration of these X-ampliconic regions and their associated genes is warranted.

"This is a collection of genes that has largely eluded medical geneticists," says Jacob Mueller, a postdoctoral researcher in Page's lab and first author of the *Nature Genetics* paper. "None of these genes has been associated with a Mendellian trait. Now that we're confident of the assembly and gene content of these highly repetitive regions on the X chromosome, we can start to dissect their biological significance."

Adds Page: "These genes are more likely to have roles in diseases that are related to reproduction, infertility, perhaps even testis cancer. There's a whole other book to be written about this aspect of the X."

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