What's mighty about the mouse? For starters, its massive Y chromosome

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A four-day-old mouse. Credit: Wikipedia/CC BY-SA 3.0

An exhaustive effort to sequence the mouse Y chromosome reveals a surprisingly large and complex biological beast, at the same time providing remarkable insight into a heated battle for supremacy between mammalian sex chromosomes.

"This is by far the most technically difficult and structurally spectacular

thing ever sequenced," Whitehead Institute Director David Page says of the mouse Y.

Page is no stranger to the sequentially challenging. More than a decade ago, Page and his lab, along with collaborators from the Genome Institute at Washington University in St. Louis, published the sequence of the human Y chromosome. Page described the human Y as a genetic "hall of mirrors" riddled with several regions of large palindromes—areas of genetic sequences that read identically backwards and forwards. Such regions render conventional sequencing approaches incapable of detecting extremely subtle genetic differences hidden among the "mirrors." In response, Page and colleagues developed an approach known as SHIMS (single-haplotype iterative mapping and sequencing) to establish a definitive reference DNA sequence of the human Y chromosome.

To tackle the mouse Y, Page and his longtime collaborators from the Genome Institute relied once again on SHIMS to see them through a painstaking journey that would take roughly 12 years from start to finish. Their findings, published online this week in the journal *Cell*, make for fascinating comparisons of structure, gene content, and evolution among the mouse Y and primate Ys, including human, rhesus macaque, and chimpanzee.

The mouse Y's sheer size, a product of what Page refers to as "outrageous gene amplification", distinguishes it from primate Ys. In fact, one segment of the long arm of the mouse Y consists of a unit of DNA 500,000 base pairs in length that has been amplified nearly 200 times. Page and colleagues found two other startling regions within the mouse Y amplicons: a pair of direct sequence repeats measuring 7 megabases (Mb), and a second pair of tandem repeats 4.5 Mb long. To put this in perspective, the previous record holder for longest sequenced repeat is a palindromic region on the human Y chromosome measuring a

mere 1.45 Mb.

The genes on the mouse Y fall into two categories: ancestral, which trace their origins back some 200 to 300 million years, when today's sex chromosomes were still ordinary autosomes; and acquired, which the Y picked up along its way to becoming functionally specialized. Like the human and primate Ys that Page's lab has sequenced, the mouse Y lost an enormous amount of its ancestral gene content over the years—an erosion that fueled the fatally flawed theory that the Y chromosome is bound for extinction.

The mouse Y's ancestral gene loss was even more profound than that found on the primate Ys. The mouse Y retains only 9 of its 639 ancestral genes, while the human Y held onto 19 of the more than 600 genes it once shared with its ancestral autosomal partner. However, the mouse more than made up for its early decay through rampant gene acquisition and amplification. Today, the mighty mouse Y carries 700 genes on a chromosome that dwarfs the human Y with its 78 genes. Strikingly, the region occupied by the acquired and amplified genes comprises nearly 97% of the mouse Y chromosome as a whole. Moreover, the Y represents a full 3% of the entire mouse genome.

"It's exciting to be able to show once again that Y chromosomes are not decaying but are innovating," says Shirleen Soh, a graduate student in Page's lab and a co-first author of the *Cell* paper. "Here's an example of a region of the Y that it is amplified to an extent that it has taken over the whole chromosome."

So how did this happen? Because all but 45 of the 700 genes on the mouse Y belong to three acquired gene families, all of which are hugely amplified, and all of which have amplified counterparts on the mouse X chromosome, Soh, Page, and former Page lab graduate student and co-first author Jessica Alföldi conclude that the X and Y have long been

exchanging genes not with each other but with themselves, in a process known as intrachromosomal recombination. While such self-exchange of genes could account for the mechanics of X and Y co-acquisition, it doesn't really explain its purpose or, for that matter, why this convergent acquisition and amplification has occurred to such an extreme.

For that explanation, the paper's authors implicate a phenomenon known as sex-linked meiotic drive, in which a "driver" arising on one sex chromosome is transmitted to subsequent generations more often than its counterpart. Theoretically, 50% of offspring are female (XX) and 50% are male (XY). However, the presence of a sex-linked meiotic drive can skew this natural 50:50 sex ratio. To counter this, the opposing sex chromosome acquires a meiotic "suppressor" aimed at restoring balance between the sexes.

Because the three amplified, acquired gene families on the mouse Y and their homologs on the mouse X are both expressed in testicular germ cells, Page envisions a scenario in which the X chromosome acquired a meiotic driver leading to enhanced success of X-bearing sperm. In retort, the Y acquired suppressors that would bolster the fitness of Y-bearing sperm. Indeed, research from other labs recently showed that mice with the Y version of one of the gene families knocked down have a higher number of female offspring; conversely, knockdown of the X version results in more male offspring. This game of point-counterpoint, however, appears to have escalated in a way not seen in the primates.

"We see strong evidence that the mouse Y and the mouse X have been engaged in hand-to-hand combat in a battle to be transmitted preferentially to the next generation," Page says. "During the making of eggs and sperm, opportunity arises for the X and Y to act upon selfish instincts."

Although this particularly extreme "arms race" between the X and Y is

specific to the mouse-rodent lineage, X-Y interchromosomal conflict may be occurring widely in mammals. Other research, for example, suggests that the cat and horse Y chromosomes have highly amplified gene families. More exploration will be needed, but Page emphasizes that having a high-quality reference sequence of the mouse Y is critical, allowing the scientific community to study sex chromosome function in a genetically manipulable model organism.

"In this age of easy genome editing, this sequence opens the door to work with the premier mammalian genetic model," says Page, whose lab recently collaborated with that of Whitehead Member Rudolf Jaenisch to perform the first targeted mutation of a Y chromosome gene. "We really are entering a new era of Y chromosome biology.

More information: "Sequencing the mouse Y chromosome reveals convergent gene acquisition and amplification on both sex chromosomes" *Cell*, October 30, 2014 (online)

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