Scientists show how men amp up their X chromosome

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What makes a man? His clothes? His car? His choice of scotch? The real answer, says Brown University biologist Erica Larschan, is the newly understood activity of a protein complex that, like a genetic power tool, gives enzymes on the X-chromosome an extra boost to increase gene expression. The process is described in the March 3, 2011, issue of the journal *Nature*.

Women have two X-chromosomes in their genomes while males have an X and a Y. Gender is defined by that difference, but for men to live, the genetic imbalance must be remedied. In mammals, cells therefore work to emphasize, or "upregulate," the lone X-chromosome in males and de-emphasize, or "downregulate," the extra X-chromosome in females.

The means by which males so freely express the genes on their X-chromosomes intrigued Larschan when she was a postdoctoral scholar in the lab of Mitzi Kuroda at Harvard Medical School and Brigham and Women's Hospital. To figure the process out, she performed experiments in the convenient model of fruitflies. In collaboration with Eric Bishop, a graduate student at Harvard and Boston University, Larschan finished the analysis at Brown, after joining the faculty as assistant professor in January 2010.

The team had a head start. Scientists already suspected that X-chromosome upregulation had a lot to do with a protein complex called MSL that binds to the X-chromosome. MSL stands for "male-specific lethal" because the mutant form would prove deadly for a male fruitfly.

What scientists didn't know was how it worked. It's not easy to double the levels of expression of a wide variety of genes on one specific chromosome.

Drilling into the X

It turns out that MSL increases gene expression on the X-chromosome by cracking open the DNA double helix more frequently. In the language of X-chromosome upregulators (a.k.a. men), it's a specialized drill bit, machined just for the X-chromosome, like a masonry bit is crafted for concrete.

Larschan and her colleagues discovered this by using a technique called "global run-on sequencing" to measure how much of an enzyme called RNA polymerase II was active in the X-chromosome. RNA polymerase II converts DNA instructions into RNA code to express genes. They found that all chromosomes have the same amount of the enzyme, to a point. After that — farther along each gene — the X-chromosome has noticeably more than other chromosomes. In other words, something allows more RNA polymerase II to move farther along the X-chromosome genes, past the point where those enzymes start to peter out on other chromosomes.

Was that something in question MSL? The team showed that it was by interfering with the MSL complex. When they did that, no greater amount of RNA polymerase persisted along the X-chromosome genes than along any other genes in the genome. Without MSL, the enzyme had lost its ability to push farther.

The finding that the regulation of gene expression occurs farther along genes on the X-chromosome is new, as is the discovery that MSL is promoting it, Larschan said.

"People had thought for a long time that most of the regulation was happening at the beginning of a gene, so this is a new step that people are just starting to think about, which is regulating the entry of polymerase into the rest of the gene," she said. "MSL is what's promoting this entry into the gene bodies."

That's one small step for MSL, and one giant leap for the manly kind who carry it.

More information: "Comprehensive analysis of the chromatin landscape in Drosophila melanogaster." *Nature* (2011).

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