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Study confirms males and females have at least one thing in common: Upregulating X

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In a study published today in the journal *Nature Genetics*, a group of scientists including UNC biologist Jason Lieb, PhD, present experiments supporting a longstanding hypothesis that explains how males can survive with only one copy of the X chromosome. The finding provides clarity to a hotly debated topic in science and provides biologists with more information to interpret experiments involving genetic measurements in males and females.

"The issue is important because many diseases are tied to a defect in a regulatory mechanism within the cell," said Lieb, who is also a member of UNC Lineberger Comprehensive Cancer Center.

Women have two X chromosomes, while men have one X and one Y. The lack of a 'back up' copy of the X chromosome in males contributes to many disorders that have long been observed to occur more often in males, such as hemophilia, Duchene muscular dystrophy, and certain types of color blindness. Having only one copy of X and two copies of every other chromosome also creates a more fundamental problem – with any other chromosome, the gene number imbalance resulting from having only one copy would be lethal. How can males survive with only one X?

Biologists have been debating how organisms and cells manage the imbalance between X and other chromosomes for years, with the dominant theory being that both sexes up-regulate the expression of X-linked genes, essentially doubling their expression to "2X" in males and

"4X" in females. Then, to correct the imbalance that now appears in females (since they have the equivalent of "4" Xs now and 2 of every other chromosome), females then 'turn off' one of the hyperactive X chromosomes, resulting in a balanced "2X" expression of those genes across both sexes.

The advent of new technology based on RNA sequencing and proteomic analysis has given scientists more accurate ways to measure gene expression, and some results published in the last few years have not supported the idea that X chromosomes up-regulate.

Lieb and his colleagues re-analyzed data used in previous analyses, along with new data from humans, mice, roundworms, and fruit flies and found more evidence that the up-regulation hypothesis is correct – but with some interesting twists across species. In mammals – humans and mice – both males and females up-regulate X chromosome gene expression and females then equalize expression by turning off the one X chromosome. In roundworms (C. elegans) the both female X chromosomes stay active, but the genes on both Xs are down-regulated by half to compensate in the females. In fruit files (Drosophilia melanogaster), males increase the expression of X chromosome genes, with no upregulation of X in females.

"There are several ways to get the same result and we are seeing how the dosage-balancing mechanism works in different species," says Lieb. "We also found that not all X-linked genes are dosage compensated to the same degree– adding another layer of complexity for scientists who study gene regulation."

Provided by University of North Carolina School of Medicine

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