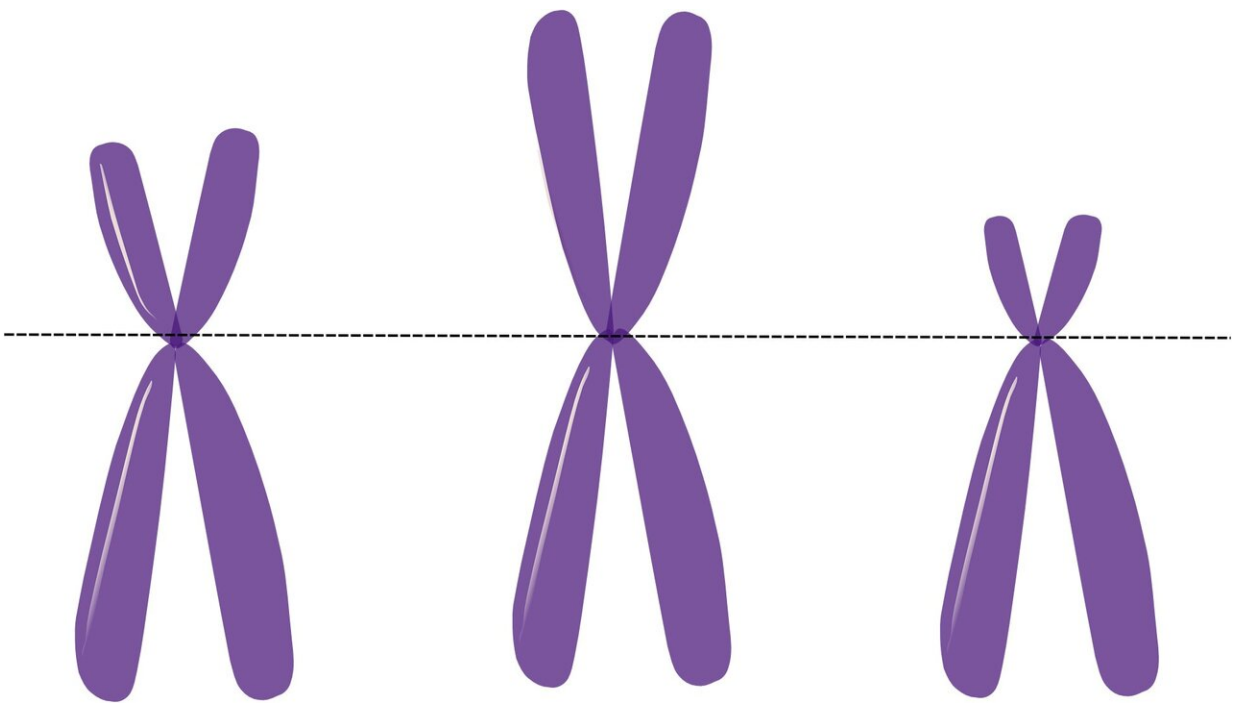


# Study reveals how two sex chromosomes communicate during female embryo development

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Researchers at Massachusetts General Hospital (MGH) have solved a mystery that has long puzzled scientists: How do the bodies of female humans and all other mammals decide which of the two X chromosomes it carries in each cell should be active and which one should be silent?

In a breakthrough study published in *Nature Cell Biology*, the MGH team discovered the role of a critical enzyme in the phenomenon known as X chromosome inactivation (XCI), which is essential for normal female development and also sets the stage for genetic disorders known as X-linked diseases (such as Rett Syndrome) to occur.

Scientists have known for over a half century that female mammals undergo XCI during embryo formation. Females have two copies of the X chromosome, and each carries many genes. Having genes expressed on both X chromosomes would be toxic to the cell, as would having both X chromosomes inactivated. To avoid these fates, females evolved with a mechanism that inactivates, or silences, one of the chromosomes.

Over the years, investigators have made strides in understanding how XCI occurs. In 2006, a team led by Jeannie Lee, MD, Ph.D., of the Department of Molecular Biology at MGH reported that during embryo development the two X chromosomes briefly come together, or pair.

She and her colleagues have since uncovered conclusive evidence that pairing is necessary for the body to decide which X chromosome to inactivate. "But until now, no one knew what one X chromosome was saying to the other to make the decision," says Lee, who is senior author of the *Nature Cell Biology* paper.

To find out, Lee and her colleagues had to develop sophisticated molecular tools that allow them to study key proteins involved in XCI, which were previously difficult to measure. It was already known that, prior to pairing, both X chromosomes are identical, or "symmetrical," meaning that they express the same genes.

Importantly, both express a form of noncoding RNA called Xist, which plays a vital role in inactivating the X chromosome. However, both X chromosomes also express another form of RNA, Tsix, which blocks

Xist and prevents XCI.

In the *Nature Cell Biology* paper, Lee and her team show that an enzyme called DCP1A randomly chooses one X chromosome to bind to, and in doing so it cuts off, or "decaps," Tsix's protective cover, making the RNA unstable. However, because DCP1A exists in tiny quantities, there is only enough to bind to one X chromosome. "DCP1A flips the switch that starts the entire cascade of X chromosome inactivation," says Lee.

As a result, a protein called CTCF—the "glue" that holds X chromosomes together during pairing—binds to the unstable Tsix RNA and causes it to shut down permanently. Xist is then able to complete the silencing of that X chromosome.

"DCP1A allows the two X [chromosomes](#) to have a fateful 'conversation'," says Lee, noting that there are many other instances where the body must choose which copy of a gene to express in order to maintain a healthy state. "This discovery," says Lee, "will help scientists understand how other molecular conversations take place in the cell."

Jeannie Lee, MD, Ph.D., of the Department of Molecular Biology at MGH, is also director of the Lee Laboratory and a professor of Genetics at Harvard Medical School. The lead author of the *Nature Cell Biology* Paper is Eric Aeby, Ph.D., a research fellow in the Lee Laboratory.

**More information:** Eric Aeby et al, Decapping enzyme 1A breaks X-chromosome symmetry by controlling Tsix elongation and RNA turnover, *Nature Cell Biology* (2020). [DOI: 10.1038/s41556-020-0558-0](https://doi.org/10.1038/s41556-020-0558-0)

Provided by Massachusetts General Hospital

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