

## New insights into the silencing of X chromosome genes passed on from fathers to daughters

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## Imprinted X-inactivation via inheritance of silencing among old genes

Credit: Molecular Cell (2024). DOI: 10.1016/j.molcel.2024.02.013



Daughters inherit two X chromosomes (one from the mother and one from the father), while sons inherent an X chromosome only from the mother. In <u>new research</u> published in *Molecular Cell*, investigators at Massachusetts General Hospital (MGH) discovered that a large part of the X chromosome that a father passes on to his daughter is silent, even before fertilization.

This may be a mechanism to balance X-linked gene activity between the sexes during early embryo development, as well as during evolution as the Y-chromosome (which started off equal to the X) lost more and more of its genetic material.

For the study, scientists analyzed the pattern and timing of gene expression in <u>mouse embryos</u>. They found that some genes on the X chromosome passed on from the father become newly inactivated during female embryo development, as previous research has shown.

Others, however, were inherited from the father in a pre-suppressed state, a finding that had not been demonstrated before, although the idea was long-postulated. Interestingly, these pre-suppressed genes tended to be the oldest in terms of their evolutionary age on the X chromosome.

"We believe that this is an ancient mechanism whereby the paternal germline ensures that sons and daughters get the same 'dose' of the X chromosome during embryogenesis. Otherwise, daughters would always have twice as many X-genes as sons, which would put male embryos at a disadvantage," explains senior author Jeannie T. Lee, MD, Ph.D., the Phillip A. Sharp Endowed Chair in Molecular Biology at MGH and a Professor of Genetics at Harvard Medical School.

"These pre-silenced genes need to be precisely controlled in embryos,



and this mechanism also avoids overdosage of X-genes in daughters," adds first author and postdoctoral fellow, Chunyao Wei, Ph.D.

It turns out that balancing sex chromosomes is even more complex, as the maternal X chromosome has to be turned up in expression in both male and <u>female offspring</u> to keep balance with the rest of the genome. Lee and her colleagues also found that hyper-activation of genes on the maternal X chromosome was timed with silencing of genes on the paternal X chromosome during female embryo development.

Therefore, when genes on the paternal X chromosome were expressed, they were moderately expressed on the maternal X chromosome, but when genes on the paternal chromosome were silenced, they were highly expressed on the maternal X chromosome. "This fine balancing act ensures that other <u>chromosomes</u>, which are always present in two copies, do not overpower the X chromosome," says Lee.

**More information:** Chunyao Wei et al, Imprinted X chromosome inactivation at the gamete-to-embryo transition, *Molecular Cell* (2024). DOI: 10.1016/j.molcel.2024.02.013

## Provided by Massachusetts General Hospital

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