Platypus and chicken reveal how chromosomes balance between the sexes

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The platypus and chicken have vastly different sex chromosome systems compared to humans—which can give us valuable insights into how our own bodies work. Credit: Shafagh Waters and Lisa Melisa

UNSW Sydney researchers have made new discoveries of fundamental differences in biological processes between males and females—by interrogating the unique and diverse sex chromosome systems of the platypus and the chicken.

The findings, published in *Proceedings of the National Academy of Sciences* (*PNAS*), are a surprise in the field of genetics. The discoveries will help build a better understanding of how sex chromosomes evolved, how our bodies function—and they could lead to new discoveries in biology.

"Mammals, such as humans, have females with two X chromosomes and males with one X chromosome and one Y chromosome, which creates an imbalance between the sexes," says lead author Dr. Nicholas Lister from UNSW's School of Biotechnology and Biomolecular Sciences.

"This imbalance is corrected by a process called sex chromosome dosage compensation."

Scientists have long known that animals have solutions to balance sex chromosome differences and achieve 'normal' function.

Dr. Lister says, "In female mammals, such as humans and mice, XX females and XY males have different numbers of the X chromosome. To balance this difference, one of the X chromosomes in females is typically silenced.

"Silencing one X chromosome in females equalizes the gene products on the sex chromosomes.

"This prevents females from producing double the number of proteins from the X compared to males."

Balancing the scales

Every cell in our bodies uses proteins to perform specific functions.

"They are translated from mRNA, which carry the instructions for cells to make proteins," the study's research lead, Associate Professor Paul Waters, also from UNSW's School of Biotechnology and Biomolecular Sciences, says.

"Being male or female affects mRNA levels of X chromosome genes, which we would then expect to affect protein production."

But A/Prof. Waters says this study demonstrates—for the first time—that a balance of proteins occurs between the sexes, even when mRNA levels aren't balanced.

"The findings suggest that dosage compensation is a crucial process in species with differentiated sex chromosomes to ensure that protein levels are balanced," he says.

"These results are significant as they suggest that dosage compensation of sex chromosomes is essential after all—and across all vertebrate species, not just placental and marsupial mammals."

Why the platypus and the chicken?

The study focused on the platypus and the chicken—two species with vastly different sex chromosome systems that offer valuable insights into the evolution and mechanisms of dosage compensation.

"Platypus are monotreme mammals, with interesting sex chromosome systems," Dr. Lister says.

"They have five pairs of X chromosomes in females and five Xs and five

Ys in males.

"Birds—such as chickens—have a ZW system, where males have two copies of a Z chromosome and females have a Z and a W chromosome."

A/Prof. Waters says the scientists had already observed near perfect sex chromosome dosage compensation of RNA between males and females in placental and marsupial mammals.

"However, in birds and monotremes, there is an imbalance of mRNA between the sexes," he says.

"This is something we thought was impossible.

"For the first time, we show that this imbalance is corrected at the protein level.

"This means that platypus and chicken have a novel mechanism of dosage compensation that is different to how we humans do it."

Are our genes really in control?

Co-author Professor Jenny Graves, from the Department of Environment and Genetics at La Trobe University, had demonstrated that genes on the inactive human X chromosome are not copied into RNA back in 1986.

Silencing at the level of RNA then became the paradigm for all epigenetic silencing.

"As the genes were silenced by their failure to make RNA, the control of dosage compensation was assumed to be at the level of RNA only—not at the level of making proteins," Prof. Graves says.

"But mRNA levels for genes on sex chromosomes weren't balanced in the platypus or the chicken," she says.

"So, scientists questioned the assumption that dosage compensation is essential for life."

A/Prof. Waters says that measuring protein levels has been a much trickier endeavor than measuring mRNA levels, due to technological challenges.

"And now that the technology is more sensitive, we can see that the dosage compensation of sex chromosomes between males and females is observed at the protein level in the platypus and the chicken," A/Prof. Waters says.

"The males and females of these species make similar amounts of proteins, despite the discrepancies in mRNA quantities."

How will this knowledge be applied?

The authors emphasize the complexity of genetic regulation and the importance of considering multiple levels of control in gene expression.

Co-author Dr. Shafagh Waters from UNSW's School of Biomedical Sciences says the study paves the way for a deeper understanding of genetic regulation.

"Studying unique species like the platypus provides us with new insights into the cellular and molecular mechanisms that could regulate various aspects of human physiology, or be implicated in disease states," she says.

"So, while these processes may not directly apply to human dosage compensation, they illuminate how our bodies manage gene expression and protein production.

"Our findings have the potential to advance knowledge in evolutionary biology and lead to innovative therapies in medical genetics.

"Understanding these mechanisms across different species can help identify new targets for diseases where protein dysfunction is key."

Dr. Lister says future research will examine the mechanisms that contribute to dosage compensation.

"This work will help us discover other dosage compensation systems in nature," he says.

"We can find out how these evolved and how they work in other species."

A/Prof. Waters says, "Understanding these processes in other species can enhance our grasp of gene regulation at a fundamental level."

More information: Nicholas C. Lister et al, Incomplete transcriptional dosage compensation of chicken and platypus sex chromosomes is balanced by post-transcriptional compensation, *Proceedings of the National Academy of Sciences* (2024). DOI: 10.1073/pnas.2322360121

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