Nature Reviews Genetics | AOP, published online 30 November 2010; doi:10.1038/nrg2921

DOSAGE COMPENSATION

What dosage compensation?

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According to a widely held view first proposed by Susumu Ohno, genes on the active mammalian X chromosome are expressed at twice the level of those present on two autosomes. A study using RNA–seq data overturns this model by showing that, in mice and humans, genes on the X chromosome are expressed at the same level as those on autosomes.

For over 40 years it has been assumed that genes on the X chromosome of mammals double their expression to make up for there being only one active copy (a single X in males and a single active X in females). Two microarray-based expression studies supported this view by showing that the ratio between expression on the X chromosome and the two autosomes (X:AA) is ~1. However, microarrays were designed for comparing the expression of the same gene across different conditions, rather than for comparing the expression levels of different sets of genes, and so they are not the most sensitive tool for testing Ohno's hypothesis. Xiong *et al.* show that RNA–seq is free from the biases that afflict microarrays, and so they used public RNA–seq data to measure the X:AA ratio in 12 human and three mouse tissues.


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They showed that the X:AA expression ratio in mouse and human is ~0.5 — that is, no dosage compensation is taking place. This is true in males and females, and applies equally to X-linked genes that emerged before and after the evolution of the X chromosome.

The results, which were confirmed by small-scale proteomics experiments, tell us something important about the evolution of the sex chromosomes. The existing model posits that, in mammals, the proto-X chromosome would have needed to double its expression level in males to match expression from the autosomes. In a second step, females would have found a way to resolve the dosage imbalance caused by having two upregulated X chromosomes. If, as is proposed in this paper, expression on the X chromosome is not upregulated in mammals, then the first of these steps did not happen, making the second step — dosage compensation — unnecessary. The data would also predict that the mammalian X chromosome contains an unusually high number of haplosufficient genes.

A different picture emerged from analysing RNA–seq data from *Caenorhabditis elegans*: the X:AA ratio in hermaphrodites (XX) had been estimated by microarrays to be ~1, but this study shows that X:AA varies during development, decreasing from 0.92 in the second larval stage to 0.41 in adults. This change is caused by an almost two-fold downregulation of X-chromosome expression over developmental time, although the mechanism by which this occurs is unknown.

After RNA–seq data become available for additional species, it will be interesting to look at how other dosage compensation mechanisms — such as those of flies and birds — stand up to scrutiny.

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ORIGINAL RESEARCH PAPER Xiong, Y. *et al.* RNA sequencing shows no dosage compensation of the active X-chromosome. *Nature Genet.* 21 Nov 2010 (doi:10.1038/ng.711)
FURTHER READING Wang, Z., Gerstein, M. & Snyder, M. RNA-Seq: a revolutionary tool for transcriptomics. *Nature Rev. Genet.* **10**, 57–63 (2009)