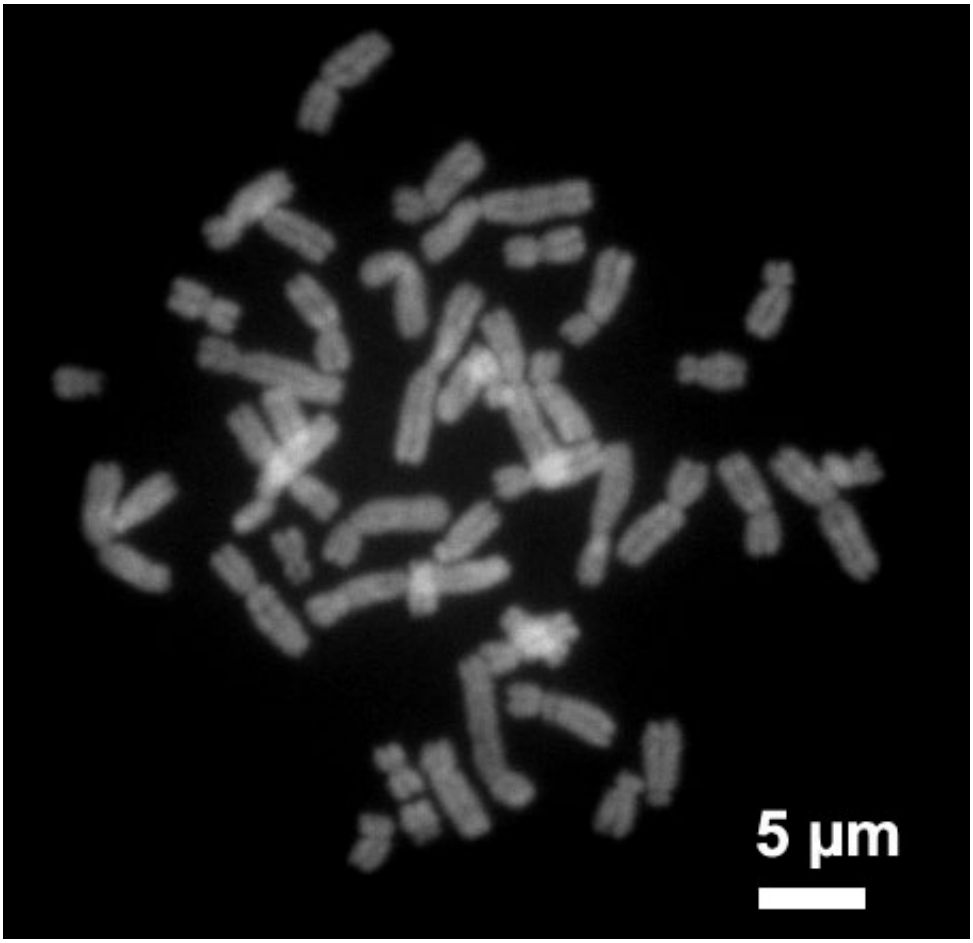
Research reveals clever dosage control mechanism of biallelic genes

November 29 2023



Human chromosomes during metaphase. Credit: Steffen Dietzel/Wikipedia

Have you ever wondered why we carry two copies of each chromosome in all of our cells? During reproduction, we receive one from each of our

parents. This means that we also receive two copies, or alleles, of each gene—one allele per chromosome or parent.

Both alleles are able to produce messenger RNA, which is the recipe needed to make proteins and keep cells running. Scientists hypothesize that having two alleles for each gene is the cell's in-built redundancy system. If there is ever a mutation or drop in messenger RNA production from the allele carried on one of the chromosomes, the allele on the second chromosome will serve as a backup and will be able to step up to produce sufficient messenger RNA output to compensate for loss of the first allele. This redundancy enables us as humans to be largely resistant to the effects of recessive mutations.

However, a class of genes known as haploinsufficient genes, rely on the continuous expression of two intact alleles. If just one allele of a haploinsufficient gene is compromised, it will lead to human disease. It was therefore hypothesized that the cell may have a special "safety" mechanism to safeguard the messenger RNA expression from this special class of genes. A study featured in the journal *Nature* led by Asifa Akhtar discovered exactly such a mechanism.

MSL2 is an epigenetic dosage-sensor

The researchers found that the epigenetic regulator MSL2 guarantees the expression of both alleles of specific haploinsufficient genes, ensuring the right messenger RNA dosage. This is crucial because genes require different dosage depending on the tissues they are expressed in. With MSL2, the team has identified, for the first time, a protein that can sense these dosage-sensitive genes and ensure their biallelic expression in the relevant tissue or developmental stage.

"We were always wondering whether the copy of the gene on the chromosome coming from the mother could communicate with the

second copy on the chromosome coming from the father. Our findings imply an underlying communication between the two alleles and we speculate that MSL2 ensures that mom and dad can talk to each other—at least molecularly," says Asifa Akhtar, Director at the Max Planck Institute of Immunobiology and Epigenetics in Freiburg.

Tracking down the allelic regulator with a genetic trick

Fascinated by their discovery of a mechanism which safeguards the biallelic expression of haploinsufficient genes, the researchers investigated how this MSL2 mechanism works at the molecular level. To tackle this, the team used a trick.

"We crossed genetically distant mouse strains with each other—a bit like crossing a Chihuahua with a Great Dane. This allowed us to see which alleles were inherited from the mother and which from the father," says Yidan Sun, the first author of the paper, explaining the method of allele-specific gene expression analysis. With this hybrid mouse system, the team could analyze the activity of individual alleles.

She adds, "In contrast to the standard method of expression data analysis, in which the gene products are summed over the two alleles, this gave us the resolution necessary to track the expression status of each allele individually."

A future for novel therapeutic strategies to address diseases

Their experiments demonstrated that when MSL2 was lost in hybrid mouse cells, certain haploinsufficient genes could only achieve monoallelic expression. This implies that in mammalian cells, MSL2 is

necessary for the biallelic expression of genes, ensuring their functionality and, consequently, the overall health of the organism. Interestingly, many of the haploinsufficient genes regulated by MSL2 are associated with neurological disorders.

"But what adds a fascinating layer to this discovery is the tissue- and cell-type specificity of these genes. Looking at the organism as a whole, it makes you wonder whether a backup system orchestrated by epigenetic factors such as MSL2 might explain why people, even with similar lifelong habits like smoking or diet, have different health outcomes or disease risks," says Meike Wiese, one of the first authors of the study.

An evolutionarily conserved mechanism that regulates gene dosage

"My lab started out studying dosage compensation in fruit flies, which is the process by which males with one X chromosome can achieve the same level of gene products as females with two X chromosomes. Over the years we have been fascinated by how male fruit flies with just one X chromosome do double duty to produce the same messenger RNA compared to the females with two X chromosomes," says Asifa Akhtar.

"Without this double dose males simply die! It looks like this strategy has been cleverly adapted by mammals. Our results clearly illustrate how the same tools, like MSL2, are again used in evolution to regulate dosage of genes. Gene dosage matters, and our study provides a new level of understanding of how the cells in our body ensure that we get the right dose of messenger RNAs."

What truly excites the scientists is that this discovery opens new directions to delve deeper into understanding the modulation of gene dosage within our cells. MSL2, as revealed, may just be one example of

such an allelic regulator, suggesting the existence of other factors performing similar roles.

This newfound knowledge carries profound implications for understanding diseases and holds promise for developing potential treatments.

More information: Asifa Akhtar et al, MSL2 ensures biallelic gene expression in mammals, *Nature* (2023). DOI: 10.1038/s41586-023-06781-3.
www.nature.com/articles/s41586-023-06781-3

Provided by Max Planck Institute of Immunobiology and Epigenetics