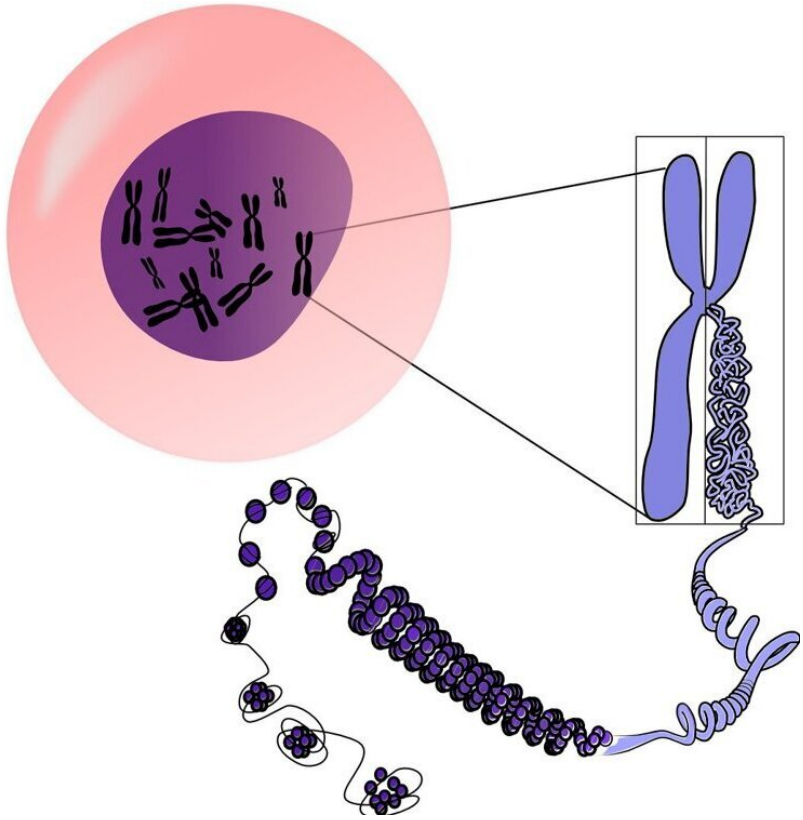
Down syndrome research should look at the whole cell, not just the extra chromosome, scientists say

December 1 2022



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Research on understanding the effect of extra chromosomes for conditions like Down syndrome typically involves examining what genes

play a role in the symptoms of these conditions. However, researchers from Germany and the U.S. propose a new way of looking at these conditions, suggesting that when an extra chromosome is present, the impact on the cell depends less on which chromosome is duplicated and more on the presence of extra DNA. This work appears in a review published December 1 in the *American Journal of Human Genetics*.

"Understanding the complexity and general nature of disease phenotypes allows us to see a bigger picture and not get stuck focusing on a single gene, due to its presence on the extra chromosome," says lead author Maria Krivega, developmental biologist at Heidelberg University.

Every cell starts out with extra chromosomes during early embryogenesis; however, this DNA gets sorted into pairs after about a week of growth. When this process goes awry, it often leads to death of the embryo, with only a few being able to survive with the extra DNA, like in the case of Down syndrome.

By taking a step back and looking at the entire cell, researchers were able to create a new understanding of these syndromes. Krivega and her collaborators took a critical look at recent evidence suggesting that Down syndrome phenotypes arise not only because of increased dosage of genes on chromosome 21 but also because of global effects of chromosome gain.

The researchers sifted through published datasets of proteins and RNA of individuals with Down syndrome and compared these to laboratory made cells with trisomies of chromosomes 3, 5, 12, and 21. What they found from this comparison was that it didn't matter which chromosome was in excess, the cells all had decreased ability to replicate, survive, and maintain their DNA.

"We were interested to find out why cells with imbalanced chromosomal

content—in other words, aneuploid—are capable of surviving," says Krivega. "It was particularly exciting to me to learn if viable aneuploid embryonic cells have similarities with aneuploid cancer cells or cell lines, derived in the laboratory."

Additionally, they found that the adaptive T cell immune system was underdeveloped in all cells, while the innate immune system seemed to be overactive. The authors suggest that this is a consequence of general chromosome gain. This research can be expanded into autoimmune diseases, such as Alzheimer disease or acute leukemias in trisomy chr. 8 or 21, that also exist without any connection to aneuploidy.

"We hope that our work elucidating a complex trisomy phenotype should help to improve such kids' development," says Krivega.

More information: Consequences of chromosome gain—a new view on trisomy syndromes, *American Journal of Human Genetics* (2022). DOI: 10.1016/j.ajhg.2022.10.014 , www.cell.com/ajhg/fulltext/S0002-9297(22)00462-1

Provided by Cell Press