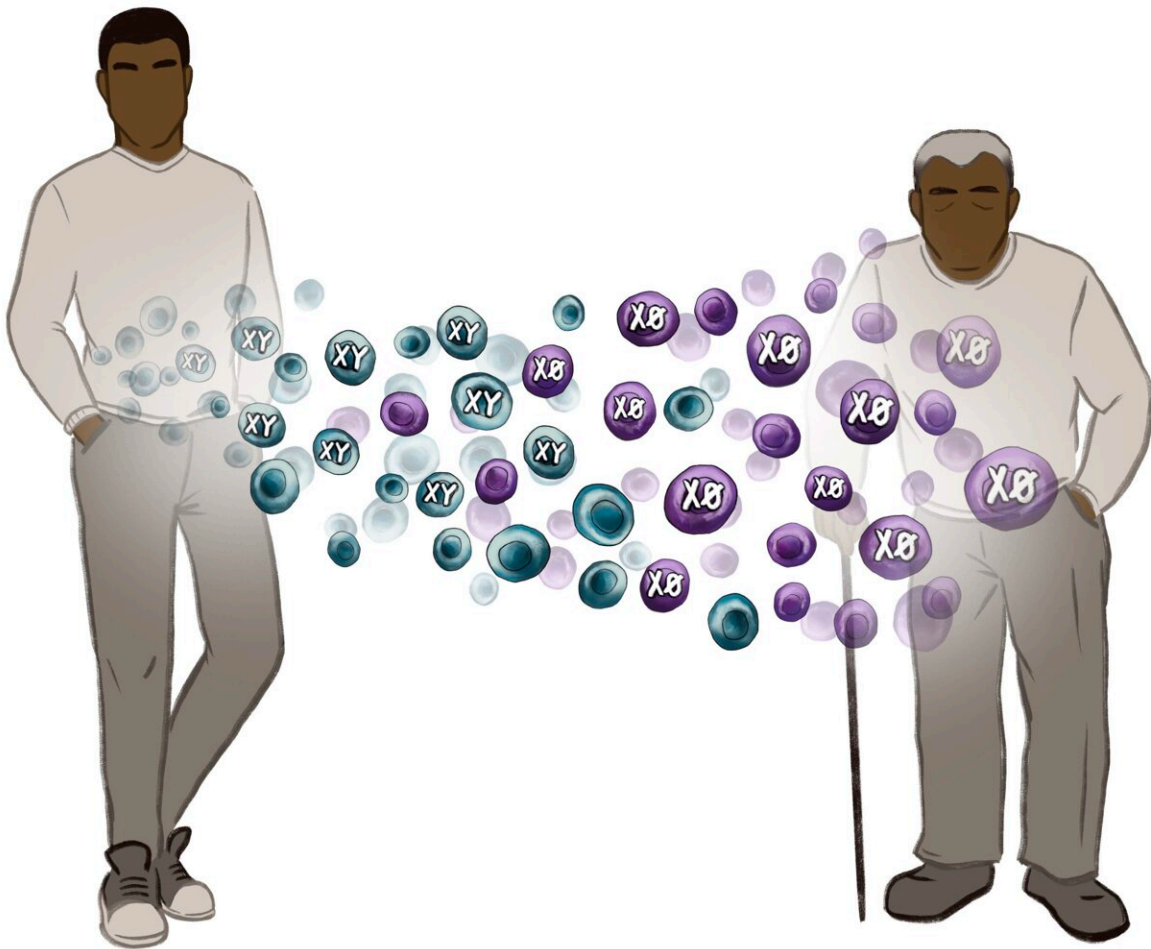


Loss of male sex chromosome leads to earlier death for men

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Men progressively lose their Y chromosome as they age -- and that could be taking a toll on their health. Credit: Katriel E. Cho.

The loss of the male sex chromosome as many men age causes the heart muscle to scar and can lead to deadly heart failure, new research from the University of Virginia School of Medicine shows. The finding may help explain why men die, on average, several years younger than women.

UVA researcher Kenneth Walsh, Ph.D., says the new discovery suggests that men who suffer Y chromosome loss—estimated to include 40% of 70-year-olds—may particularly benefit from an existing drug that targets dangerous tissue scarring. The drug, he suspects, may help counteract the [harmful effects](#) of the chromosome loss—effects that may manifest not just in the heart but in other parts of the body as well.

On average, women live five years longer than men in the United States. The new finding, Walsh estimates, may explain nearly four of the five-year difference.

"Particularly past age 60, men die more rapidly than women. It's as if they biologically age more quickly," said Walsh, the director of UVA's Hematovascular Biology Center. "There are more than 160 million males in the United States alone. The years of life lost due to the survival disadvantage of maleness is staggering. This new research provides clues as to why men have shorter lifespans than women."

Chromosome loss and heart health

While women have two X chromosomes, men have an X and a Y. But many men begin to lose their Y chromosome in a fraction of their cells as they age. This appears to be particularly true for smokers. The loss occurs predominantly in cells that undergo rapid turnover, such as blood cells. (Loss of the Y chromosome does not occur in male reproductive

cells, so it is not inherited by the children of men who exhibit Y chromosome loss.) Scientists previously observed that men who suffer Y chromosome loss are more likely to die at a younger age and suffer age-associated maladies such as Alzheimer's disease. Walsh's new research, however, is believed to be the first hard evidence that the chromosome loss directly causes harmful effects on men's health.

Walsh, of UVA's Division of Cardiovascular Medicine and the Robert M. Berne Cardiovascular Research Center, and his team used cutting-edge CRISPR gene-editing technology to develop a special mouse model to better understand the effects of Y chromosome loss in the blood. They found that the loss accelerated age-related diseases, made the mice more prone to heart scarring and led to earlier death. This wasn't the result of just inflammation, the scientists determined. Instead, the mice suffered a complex series of responses in the immune system, leading to a process referred to as fibrosis throughout the body. This tug-of-war within the [immune system](#), the researchers believe, may accelerate disease development.

The scientists also looked at the effects of Y chromosome loss in human men. They conducted three analyses of data compiled from the UK Biobank, a massive biomedical database, and found that Y chromosome loss was associated with [cardiovascular disease](#) and heart failure. As chromosome loss increased, the scientists found, so did the risk of death.



Kenneth Walsh, PhD, of the University of Virginia School of Medicine, has found that the loss of the male sex chromosome as many men age causes the heart muscle to scar and can lead to deadly heart failure. The finding may help explain why men die, on average, several years younger than women. Credit: Dan Addison, UVA Communications

Potential treatment

The findings suggest that targeting the effects of Y chromosome loss could help men live longer, healthier lives. Walsh notes that one potential treatment option might be a drug, pirfenidone, that has already been approved by the federal Food and Drug Administration for the treatment of idiopathic pulmonary fibrosis, a form of lung scarring. The drug is also being tested for the treatment of heart failure and chronic

kidney disease, two conditions for which tissue scarring is a hallmark. Based on his research, Walsh believes that men with Y chromosome loss could respond particularly well to this drug, and other classes of antifibrotic drugs that are being developed, though more research will be needed to determine that.

At the moment, doctors have no easy way to determine which men suffer Y chromosome loss. Walsh's collaborator Lars A. Forsberg, of Uppsala University in Sweden, has developed an inexpensive polymerase chain reaction (PCR) test, like those used for COVID-19 testing, that can detect Y chromosome loss, but the test is largely confined to his and Walsh's labs. Walsh, however, can foresee that changing: "If interest in this continues and it's shown to have utility in terms of being prognostic for men's disease and can lead to personalized therapy, maybe this becomes a routine diagnostic test," he said.

"The DNA of all our cells inevitably accumulate mutations as we age. This includes the loss of the entire Y chromosome within a subset of cells within men. Understanding that the body is a mosaic of acquired mutations provides clues about [age-related diseases](#) and the aging process itself," said Walsh, a member of UVA's Department of Biochemistry and Molecular Genetics. "Studies that examine Y chromosome loss and other acquired mutations have great promise for the development of personalized medicines that are tailored to these specific mutations."

The researchers have published their findings in the journal *Science*.

The team consisted of Soichi Sano, Keita Horitani, Hayato Ogawa, Jonatan Halvardson, Nicholas W. Chavkin, Ying Wang, Miho Sano, Jonas Mattisson, Atsushi Hata, Marcus Danielsson, Emiri Miura-Yura, Ammar Zaghlool, Megan A. Evans, Tove Fall, Henry N. De Hoyos, Johan Sundström, Yoshimitsu Yura, Anupreet Kour, Yohei Arai, Mark

C. Thel, Yuka Arai, Josyf C. Mychaleckyj, Karen K. Hirschi, Forsberg and Walsh.

More information: Soichi Sano et al, Hematopoietic loss of Y chromosome leads to cardiac fibrosis and heart failure mortality, *Science* (2022). DOI: [10.1126/science.abn3100](https://doi.org/10.1126/science.abn3100).
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