As Y Chromosomes Vanish With Age, Heart Risks May Grow

A study of mice might explain why.

By Gina Kolata

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It's been known for more than half a century that many men lose their Y chromosomes as they age. But no one knew if it really mattered. The loss of Y could just be a sign of aging, like gray hair, with no clinical relevance.

Now, though, researchers report that it can matter. Very much.

A new study using male mice genetically engineered to lose their Y chromosomes provides insight. The paper, published on Thursday in the journal Science, found that when the Y chromosome was gone from blood cells in those mice, scar tissue built up in the heart, leading to heart failure and a shortened life span.

Because there was a direct cause-and-effect relationship between the loss of Y and ailments of aging in the mice, the study bolsters the notion that the same thing can happen in human males. Researchers have documented an increase in risk for chronic diseases like heart disease and cancer related to loss of the Y chromosome in many studies over the years, including the new one, which used data from a large genetic study of the British population. The loss of Y could even account for some of the difference between the life spans of men and women, the authors of the Science study say.

Other investigators not associated with the work were impressed.

"The authors really nailed it here," said Dr. Ross Levine, the deputy physician in chief for translational research at Memorial Sloan Kettering Cancer Center. "It's super important work."

The inspiration for the new research came when Lars Forsberg, a researcher at Uppsala University, ran into a former professor on a bus in Uppsala, Sweden, in 2013. They began talking, and the professor told Dr. Forsberg that the Y chromosomes in fruit flies were more important than previously appreciated.

Dr. Forsberg was intrigued. He had never paid much attention to the loss of Y chromosomes. Males have one X and one Y (females have two X's), and nearly all the genes used by male cells are genes on the X. Dr. Forsberg had shared the common view that the Y chromosome was pretty much a genetic wasteland.

At least 40 percent of males lose the Y chromosome from some of their blood cells by age 70. And by age 93, at least 57 percent have lost some of it.

The chromosome is lost sporadically from blood cells during cell division, when it is kicked out of some cells and then disintegrates. The result is what researchers call a mosaic loss of Y.

There is no way, other than to stop smoking, to reduce the risk of losing the Y chromosome. And the condition is unrelated to men having lower levels of testosterone in their bodies as they age. Taking testosterone supplements would have no effect, nor would it reverse the consequences.

Curious about the idea his professor had proposed, Dr. Forsberg went back to his computer and looked at data on 1,153 aging men in a large Swedish study, the Uppsala Longitudinal Study of Aging Men.

“I had the data in a few hours and I was like, ‘Wow,’” Dr. Forsberg said. “I saw that men with loss of Y in a large proportion of their blood cells survived only half as long, 5.5 years versus 11.1 years.”

“You can imagine my surprise,” he said. “Of course I redid everything.”

The finding held up and he published a paper in the journal Nature Genetics in 2014, reporting that increased death rates and cancer diagnoses were associated with a loss of the Y chromosome in blood cells.

He quickly founded, and became a shareholder in, the company Cray Innovation to test men for loss of Y.

Other researchers began publishing similar analyses. Soon, about 20 independent papers showed associations between loss of the Y chromosome in blood cells and heart disease, shortened life spans and various age-related diseases like solid tumors and blood cancers.

At that point, Dr. Forsberg heard from Kenneth Walsh, the director of the Hematovascular Biology Center at the University of Virginia School of Medicine. Dr. Walsh had become interested in the loss of Y chromosomes because of his work on a different type of genetic loss that occurs with aging: an increase in cancer mutations in blood cells called CHIP. People with CHIP have a greater risk of heart disease and cancer, which prompted Dr. Levine to set up a CHIP clinic at Sloan Kettering.

In January, Dr. Pradeep Natarajan, the director of preventive cardiology at Massachusetts General Hospital, and others formed a company, TenSixteen Bio, to develop a cost-effective test for CHIP and to study treatments to prevent its consequences.

But, Dr. Walsh noted, CHIP mutations are only a small part of the genetic alterations that occur with aging.

“What’s the rest of this pie?” he asked. He wondered about Y chromosomes and began planning a way to see if there was a direct cause and effect between loss of Y in blood cells and diseases. That led to his study with mice.

At first the mice seemed fine, Dr. Walsh said, but “they aged poorly.” Their life spans were shortened and they developed scar tissue in their hearts, kidneys and lungs, including non-ischemic heart failure, a type that is not the result of a heart attack and whose cause is poorly understood. The animals’ mental abilities also were diminished.

Working with Dr. Forsberg, Dr. Walsh then examined data from the UK Biobank involving 223,173 men.

Men with mosaic loss of Y had a 41 percent increased risk of dying from any cause during a seven-year follow-up and a 31 percent increased chance of dying from any cardiovascular disease. The more cells that lost Y chromosomes, the greater the risk.

But the work also raises the question, What about women? Do they lose one of their two X chromosomes? And what about women with Turner syndrome? They are born with only one X chromosome, making all their cells the equivalent of the random group of blood cells in men who lose their Y.

Women can lose an X chromosome as they age, Dr. Walsh said, but not as often as men lose their Y. Except for an association with lymphoid leukemia, the UK Biobank data has not shown health risks for women who have lost an X. But more studies are needed, Dr. Walsh said.

Turner syndrome is different. Women with the condition actually have some of the same health risks as men who have lost their Y chromosomes — cardiovascular abnormalities and non-ischemic heart failure. Their average life span is shorter than that of women with two X’s.

It is too soon to say what men should do — other than to stop smoking — to protect themselves from losing their Y chromosomes or to alleviate the consequences.

Those in Dr. Walsh’s group found they could protect the hearts of the mice without Y chromosomes by blocking TGF-beta, a key molecule involved in the production of scar tissue.

Dr. Stephen Chanock, the director of the division of cancer epidemiology and genetics at the National Cancer Institute, said the mouse study was “really cool.” But he noted that there was no evidence yet that drugs to block TGF-beta would be effective in men who lost their Y.

And, for now, there is little point in testing men for loss of Y, Dr. Chanock said, adding, “the over-interpretation of these data for monetary purposes worries me deeply.”

Gina Kolata writes about science and medicine. She has twice been a Pulitzer Prize finalist and is the author of six books, including “Mercies in Disguise: A Story of Hope, a Family's Genetic Destiny, and The Science That Saved Them.”
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