The hapless male Y chromosome finally has a purpose

I've never been fond of the human Y chromosome. Yes, the all-important *SRY* gene sets the early embryo on a path towards maleness, but the rest? Mostly DNA borrowed from a long-ago X, peppered with eight long palindromes.

"The Y is a pathetic little chromosome with lots of junk. It is gene-poor, prone to deletion, and useless. You can lack a Y and not be dead, just female," Jennifer Marshall Graves told me years ago when I defiled the Y in The Scientist. She's professor emeritus of Australian National University, an evolutionary geneticist who works on kangaroos, platypus, Tasmanian devils, and various dragon lizards.

But men missing the Y in some of their white blood cells face heightened health risks. That was a mere association a few years ago, but now appears to be causal, according to results of an investigation in Science from researchers at Uppsala University. The research combines clues from mouse studies and epidemiological data from the UK Biobank.

Male bodies come to be mosaics for the Y when the chromosome is lost as certain bone marrow cells divide, and the loss is perpetuated in the blood cells that descend from the marrow cells. The phenomenon is called mosaic Loss Of Y, or mLOY. It affects at least 20% of 60-year-olds and 40% of 70-year-olds: common and age-related.

The precarious nature of losing the Y has been associated with blood cancers, strokes, heart attacks, solid tumors, and/or Alzheimer's disease. The new study adds cardiovascular diseases, which may partly explain why men are more likely to die of these conditions than women. If the link holds up, perhaps men whose cells have dropped their Ys can focus more on controllable risk factors, like diet and exercise.

The Maligned Y

The puny Y chromosome has long had an image problem that transcends species.

A male grasshopper lacks a Y, and a male bee stems from an egg that the queen deemed unfertilizable. Turtle eggs laid in the sun become sisters, their shaded brethren, brothers. And the two types of mammals that don't have Ys – mole voles – are apparently fine. They even have sex.

The Y taint dates to 1965, when British geneticist Patricia Jacobs discovered that seven of 197 inmates at a high-security prison in Scotland had an extra Y. Similar investigations ensued into other unsavory places where additional Ys might lurk.

Newsweek 's cover trumpeted "congenital criminals." Newborn screens for the dreaded violent Y ensued in several nations, with psychologists dispatched to the homes of the marked infants to offer "anticipatory

guidance.” By 1974, research revealed that all the extra Y may confer is height, acne, and learning disabilities.

Meanwhile, geneticists searched for Y-linked traits – the X has 1400 or so genes, the Y a mere handful. So unevenly endowed are the sexes that female mammals shut off an X in each cell.

Searches for Y-linked traits didn’t turn up much. For years the only one was hairy ears, until girls with the trait were found hidden away.

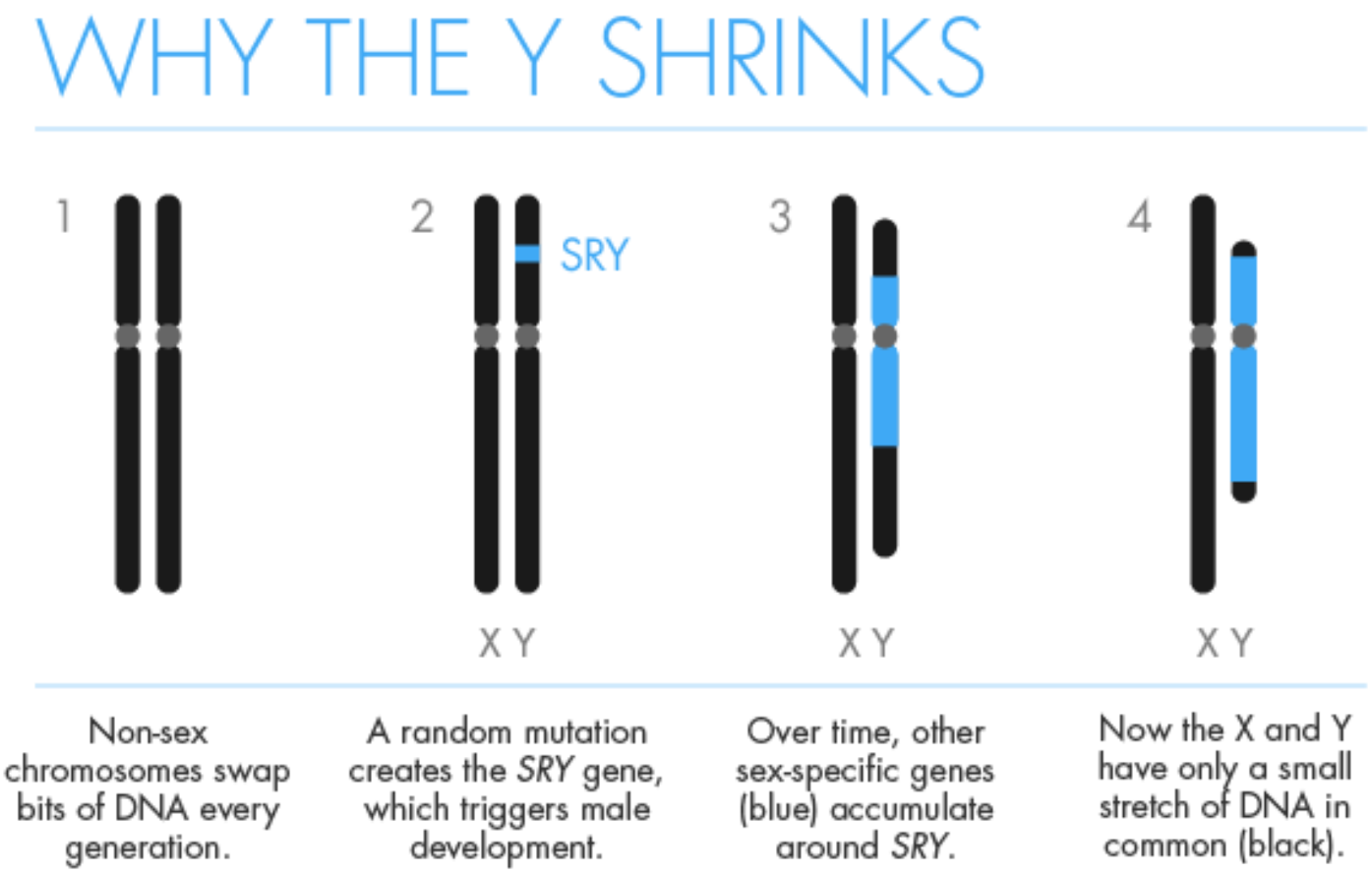
Fortunately, Jane Gitschier, professor emeritus at the University of California, San Francisco, famously took a behavioral approach, mapping such Y-linked traits as “spitting (P2E)” and “air guitar (RIF),” which mutates to “air violin” by middle age. Inability to ask for directions is another.

Circa 1990, the *SRY* gene, the hallmark of Y’s maleness, was found. When we XXs neared the end of the embryonic period, our lack of *SRY* catapulted us towards femaleness. But being female is hardly the default option developmental biologists once considered it to be; a suite of genes turns on as our parts unfurl, fold, and elaborate.

Shrinkage

Besides the *SRY* gene, a human Y doesn’t hold much valuable information, or so we thought. The few known genes were concerned mainly with sex. Even those genes might be ephemeral, according to Marshall Graves’ body of work.

She’s best known for her discovery that the human Y chromosome is inexorably shrinking. She found, in several species, a gradual exodus of genes from the Y to other chromosomes (about five genes per million years), prompting her to predict the eventual demise of the little chromosome that could.



Credit: Quanta

That panicked David Page, MIT biologist, director of the Whitehead Institute, and mapper of the part of the Y that endows maleness. Said he of Marshall Graves' findings, "It truly frightened the people in my lab."

Page often tells the sad tale of the Y. Here's a recounting from 2003:

> Back 300 million years ago, when we were reptiles, we had no sex chromosomes, only ordinary autosomes. Shortly after our ancestors parted company with the ancestors of birds, a mutation arose on one autosome to give rise to *SRY*. Shutting down XY crossing over began, in the vicinity of *SRY*, and then in an expanding region.

And that spawned problems.

"Y genes are not protected because they have lots of areas of no crossing over. Genes decayed, except for *SRY* and the chromosome tips," Page said.

Crossing over is when paired chromosomes swap parts – it's common. But the Y had to stop sharing itself with the X to attain autonomy. So the Bible had it wrong; woman didn't arise from man's rib; males arose from a borrowed bit of an X chromosome.

Page's team, years ago, discovered the exquisite symmetry of the Y, including eight massive palindromes that tangled up early sequencing efforts. By chopping the Y into tiny bits, Page discovered that many Y parts had a copy elsewhere on the Y, and that corresponding segments from one Y could be copied onto the other. So the Y, in essence, fights shrinkage by having sex with itself.

Marshall Graves dubbed the newly recognized phenomenon "a desperate race to stave off disappearing altogether." The new findings suggest that rather than being doomed to shrinkage, the Y may actually do something vital.

Y Loss Raises Risk of Death from Heart Fibrosis

It's been known for a few years that men who lose Y chromosomes in some white blood cells – indicating Y loss in bone marrow stem cells, where blood comes from – have increased incidence of heart damage and death from cardiovascular diseases. The direct culprit is fibrosis, which is the accumulation of fibroblasts (connective tissue cells) and the strands of sticky collagen and stretchy elastin proteins they secrete. A scar is born. Fibrosis increases all over in an aging body.

The researchers nailed the mechanism by using CRISPR to jettison Y chromosomes in mice. "Mice with mLOY showed an increased scarring of the heart. mLOY causes the fibrosis, which leads to a decline in heart function," said researcher Lars Forsberg. Y-less mice didn't live as long as genetically-matched mice that retained their Ys.

Epidemiological studies support the mouse work.

"Men with a higher proportion of white blood cells with mLOY in the blood have a greater risk of dying from cardiovascular disease. This observation is in line with the results from the mouse model and suggests that mLOY has a direct physiological effect also in humans," said Forsberg.

Data from the UK Biobank on more than 15,000 men revealed that those with mLOY in their blood had a 30% increased risk of dying from heart failure and related conditions during 11 years of follow-up.

Even more intriguing, the nature of the link between loss of the Y and heart disease suggests repurposing at least four drugs, and possibly others in development.

Oozing out of the bone marrow are Y-less cardiac macrophages, big, blobby white blood cells that wander the tissues and engulf pathogens. They're a key part of the innate immune response, what happens before the body launches an antibody attack.

But when Y-poor macrophages enter the heart, they hike a signaling pathway (transforming growth factor ?1 [TGF-?1)]) that prompts proliferation of fibroblasts. Scar tissue accumulates, gumming up the cardiac

works. Some TGF-?1 inhibitor drugs block the runaway fibrosis signal, possibly reversing the heart damage.

And there might be even more drug options. “The link between mLOY and fibrosis is very interesting, especially given new treatment strategies for heart failure, pulmonary fibrosis, and cancers that counteract the onset of fibrosis. Men with mLOY could be a patient group that responds particularly well to such treatment,” said Forsberg.

Coda

I love this study. It includes an animal model and human data, with a huge sample, and the proposed mechanism makes sense. It also connects the dots and may save lives.

“Several unexpected links between the Y chromosome, immune system, and complex polygenic traits have been discovered, suggesting an influence of the Y chromosome on immune and inflammatory responses in men,” write Andreas Zeiher and Thomas Braun in a Perspective accompanying the report. “The study … reinforces this view and uncovers a crucial function of the Y chromosome in maintaining a healthy innate immune system.”

I’m glad that the tiny Y has gone from a “genetic wasteland” to crucial. Even if I don’t have one.

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