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Renegade genes caught red handed

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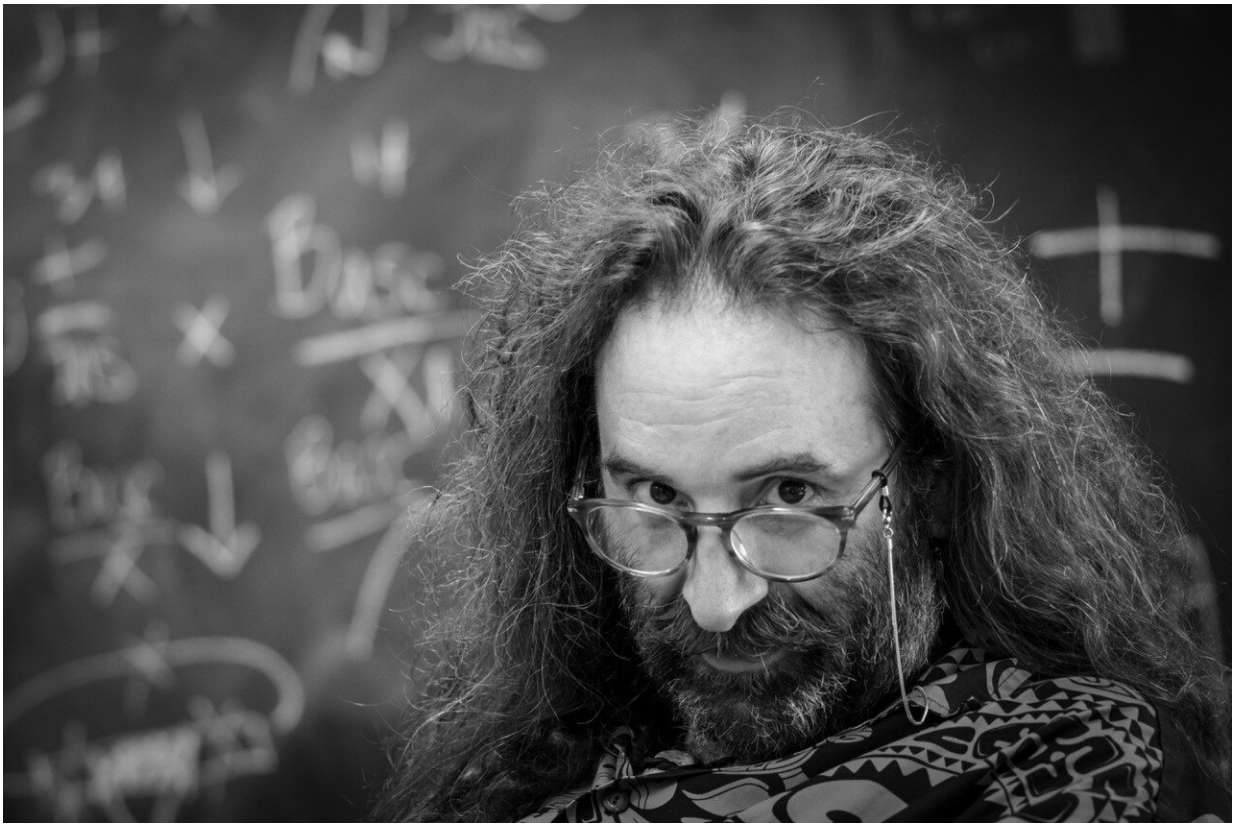

Potentially dangerous genes embedded within human DNA were once thought to be locked down by helpful DNA structures called heterochromatin. A University of Arizona researcher disputes that belief and hopes to change the paradigm even further. Credit: Kelvin Pond

The guardians of the human genome that work to prevent potentially disease-causing gene expression might not be as effective at their jobs as

previously thought, according to new University of Arizona research.

Human chromosomes are made up of DNA, about half of which includes ancient remnants of a type of virus called transposons. Also known as "jumping genes," transposons have the potential to attack other parts of the genome and cause mutations and damage if they're ever free to be expressed.

"To keep transposons from disrupting how our genes function, cells create a structure called heterochromatin," said Keith Maggert, UA associate professor of cellular and molecular medicine and member of the UA Cancer Center.

Heterochromatin, the guardian that basically handcuffs the dangerous transposons in a compact tangle of DNA strand, prevents transposons from being copied or expressed. But researchers are still working to understand the fundamentals of heterochromatin, and much of what is thought is based on assumption, Maggert said.

One assumption was that once heterochromatin formed on a transposon, it was stable, locked up for good. But research done by Maggert and his team suggests that even early on, some cells fail to silence the transposons, and even the silenced ones aren't completely quiet.

"People thought heterochromatin was good at its job," said Maggert, lead author on the paper published today in the journal *Proceedings of the National Academy of Sciences*. "But heterochromatin makes mistakes, and so it slips from time to time, flickering on and off constantly. Each time it drops the ball, we're at risk, and certain environmental conditions can lead to increased instability."

It's Maggert's ongoing hypothesis that transposons can do their damage as heterochromatin flickers on and off and becomes unstable, allowing

for errors in DNA transcription and, ultimately, the emergence of diseases such as cancer. More research is required to confirm this linkage, Maggert stressed.

Until now, studies were only able to assess how genes were expressed at the end of a fruit fly's life, but the team's novel methods allowed for the observation of heterochromatin activity throughout cell development.

"We designed a system to track the history of silencing (flickering) throughout an organism's life," Maggert said. "Imagine a game of pinball. Before, we could only see if the ball finally went in the hole, but we couldn't see all the interesting stuff—the ball bounce against the weird bumpers, what path it took, what it did before reaching that final state. The flickering on and off was a total mystery no one expected."

It took the team years to create the experiment, which consisted of a combination of biological observations of fruit flies, a novel mathematical model and genes borrowed from yeast, jellyfish and coral. It took four years to make, but just 24 hours to get the results, which have implications for how human heterochromatin functions.

"It was an exciting day, but it was also a very scary day to come in and look at the results," Maggert said.

Not only has his team learned that heterochromatin is surprisingly unstable, but "the very unusual thing about heterochromatin is it seems to 'remember' whether it's been strong or weak (handcuffed or not) even after a cell divides," Maggert said. "It's wiped away during cell division then restored afterward. This is called epigenetics—the term for silencing transposons."

No one yet understands how it happens.

"I've always been fascinated by the idea of epigenetics, and when I started working on it as a graduate student, I was totally on board. But as I've done more and more research—it's now been 20 years—I think it's all wrong," he said. "How did I lose the faith? Memory requires a mechanism, and a lot of smart people have been looking for one for 20 years and have come up empty handed. Lack of evidence is not the evidence of the lack, but at some point, you start to think, maybe we won't find it."

Next, Maggert, who is in year three of a five-year $2.5 million Transformative Research Award grant from the National Institutes of Health, hopes to complete a study where he explains how heterochromatin memory works without invoking epigenetics.

More information: Farah Bughio el al., "Monitoring of switches in heterochromatin-induced silencing shows incomplete establishment and developmental instabilities," *PNAS* (2019). www.pnas.org/cgi/doi/10.1073/pnas.1909724116

Provided by University of Arizona