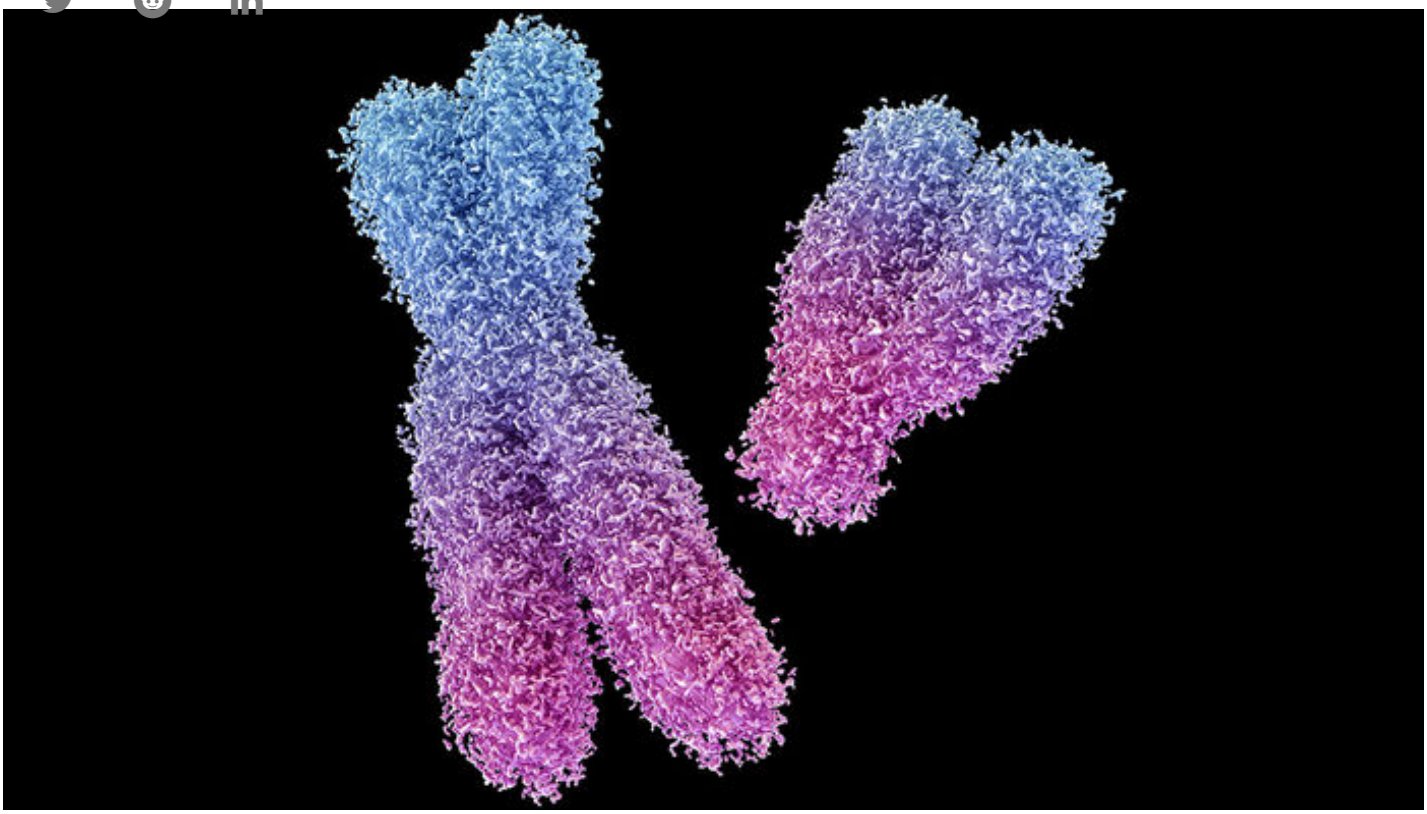

The XY chromosome combination defines a boy, but a tiny piece of regulatory DNA makes it happen. MAURIZIO DE ANGELIS/SCIENCE SOURCE

The little piece of DNA that makes girls boys

By **Elizabeth Pennisi** | Jun. 14, 2018 , 2:00 PM

What if you could flip a single DNA switch and make a world of only women? That sci-fi vision is unlikely to become reality anytime soon, yet such a switch—one near the gene that prompts the development of male body parts in embryos—has just been discovered in mice. The finding could help explain why some human babies with a male chromosome are born female, and the "groundbreaking" method used to unearth this so-called enhancer might one day identify similar DNA switches that are key to a variety of diseases.

"This is pinpointing a region that was a needle in a haystack," says Vincent Harley, a molecular geneticist at the Hudson Institute of Medical Research in Clayton, Australia, who was not involved in the new study. "[The switch] seems alone to be able to do the job" of making a man.

If left to their own devices, all human embryos would develop into girls. But a gene on the Y chromosome, named *SRY*, brings about a change in early development, causing testes, a penis, and other male traits to form. This gene indirectly turns on another gene called *Sox9*, which kick-starts the construction of the testes. Although developmental biologists have long known that one or more enhancers flips on *Sox9* early in this process, they were at a loss to figure out exactly which ones were most important. Across the genome **about 1 million enhancers** control nearly 21,000 genes. These short pieces of DNA lie outside a gene but serve as landing spots for the proteins that turn that gene on or off.

Enhancers for the *Sox9* gene are scattered across 2 million bases. So Robin Lovell-Badge, a developmental biologist at The Francis Crick Institute in London worked with Danielle Maatouk and her team at Northwestern University in Chicago, Illinois, to use multiple techniques to find them, including new methods that seek out places where enhancer-activating proteins stick to DNA or the places where DNA has unfolded a little to make way for these proteins. (Maatouk died of cancer 2 years ago.) He and his team looked for these stretches of DNA in mouse embryos just prior to and shortly after their sex was established.

The researchers found 16 good candidates for the *Sox9* enhancer. With other tests, they homed in on one that was 557 bases long and located half a million bases away from the gene itself. To turn on its target gene, such a distant enhancer is brought in contact with the gene by the looping of the chromosome they are both on.

When the researchers knocked out that enhancer in mice, *Sox9* was less active, and **the switch to male never occurred**, Lovell-Badge's team reports today in *Science*. "It is the amazing set of experimental approaches that were used in the paper that really make it groundbreaking," says Blanche Capel, a developmental biologist at Duke University in Durham, North Carolina.

About one in every 5500 human babies born has some problem related to its gender. Some have the male chromosome but no testes, for example, and doctors can figure out the reason for these abnormalities in fewer than half of all cases. Now, they can check to see whether the human version of this enhancer is disrupted in some way, Capel says. Harley, for example, has already started looking at the genomes of his patients to see whether their unexplained sex determination problems can be traced to this switch.

"It's so important in mice, it's probably important in humans as well," Lovell-Badge says. "It may be that you could use this [finding] to understand, and perhaps actually change, the gonad function." Capel predicts an even broader impact of the enhancer-finding methods. The approach taken "may be a way of defining what might be causal for diseases."

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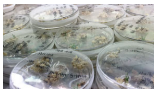

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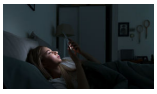

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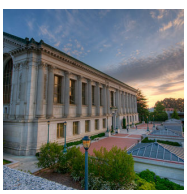

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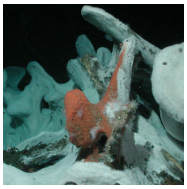

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