NATURE | NEWS

Mice with just two 'male' genes father babies

Assisted-reproduction technique helps mice with two genes from Y chromosome make healthy offspring.

Erika Check Hayden

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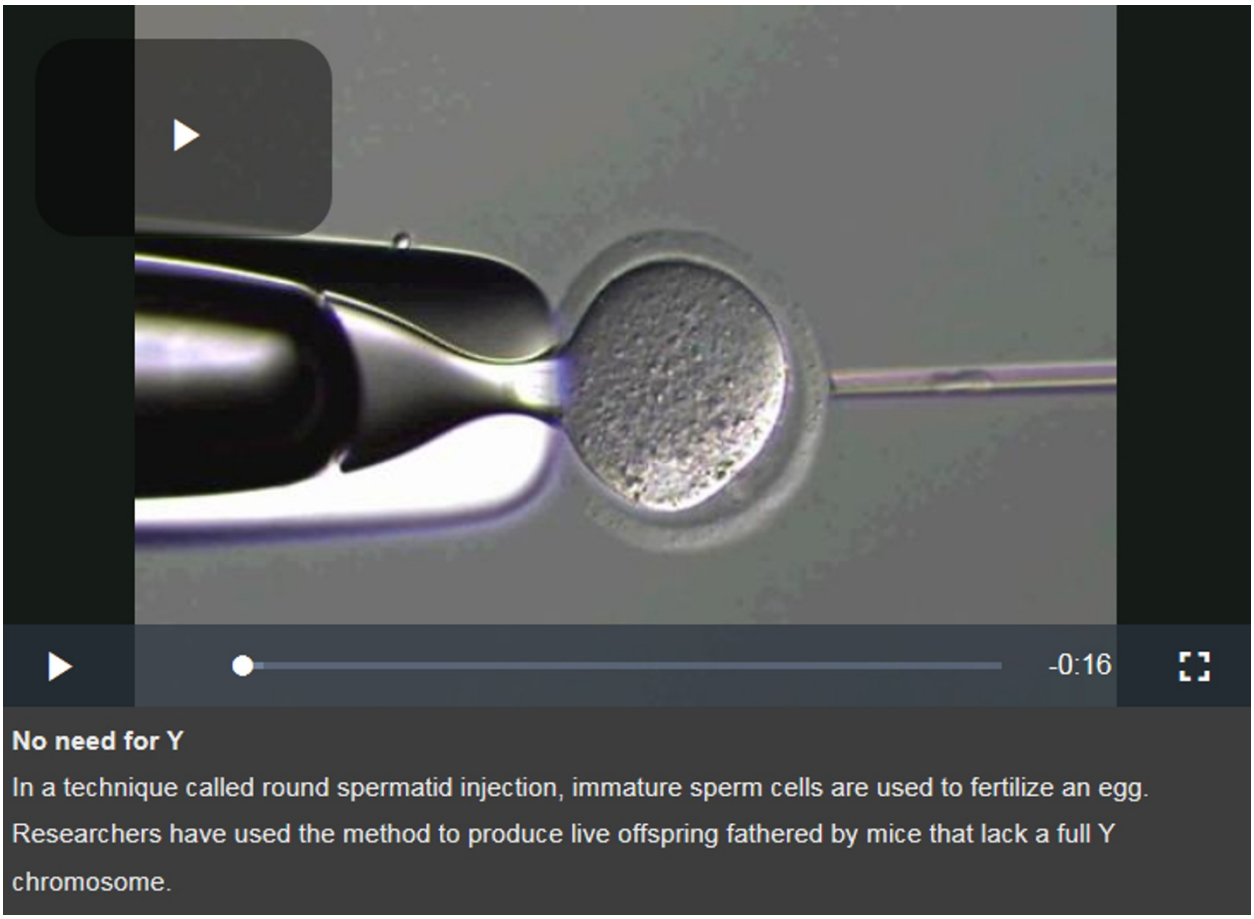

Researchers have shown that just two genes from the Y chromosome — that genetic emblem of masculinity in most mammals — are all that is needed for a male mouse to sire healthy offspring using assisted reproduction. The same team had previously reported[1] that male mice with only seven genes from their Y chromosomes could father healthy babies.

The study brings researchers one step closer to creating mice that can be fathers without any contribution from the Y chromosome at all. The findings also have implications for human infertility, because the work suggests that the assisted-reproduction technique used in the mice might be safer for human use than is currently thought.

“To me it is a further demonstration that there isn't much left on the poor old Y chromosome that is essential. Who needs a Y?” says Jennifer Marshall Graves, a geneticist at the La Trobe Institute of Molecular Science in Melbourne, Australia, who was not involved in the research.

An embryo without a Y chromosome normally develops into a female, but biologists have long questioned whether the entire chromosome is necessary to produce a healthy male. A single gene from the Y chromosome, called *Sry*, is known to be sufficient to create an anatomically male mouse — albeit one that will be infertile because it will lack some of the genes involved in producing sperm — as researchers have shown by removing the Y chromosome and inserting *Sry* into other chromosomes.

Why it takes two

More recently, researchers led by Monika Ward of the University of Hawaii in Honolulu have shown that with just two Y chromosome genes, *Sry* and *Eif2s3y*, male mice lacking a Y chromosome can at least produce sperm-cell precursors known as round spermatids (albeit not mature sperm).

In the latest study, published in *Science* this week[2], the team got these mice to reproduce, with some help. They injected the round spermatids into eggs in culture dishes in a technique called round spermatid injection (ROSI). Some of the eggs developed into embryos and were implanted into the wombs of female mice. From these transfers, 9% resulted in the birth of live mice, compared with 26% of transfers from mice with a full Y chromosome.

ROSI has been used as an assisted-reproduction technique to help infertile men whose testes cannot produce normal sperm, only spermatids. But fertility specitalists consider it an experimental procedure because of fears that immature round spermatids would contribute to the birth of genetically defective offspring. In particular, there has been concern that genetic processes such as imprinting — the switching on and off of genes that occurs in sperm cells before they come into contact with the egg — is incomplete in spermatids.

The current study could help to alleviate those fears, says developmental geneticist Robin Lovell-Badge of the Medical Research Council's National Institute for Medical Research in London. “The fact that normal offspring were obtained using ROSI with just *Sry* and *Eif2s3y* suggests that concerns about using ROSI in humans with respect to imprinting defects are probably unfounded,” he says. “This in itself is important,” both for men with defective Y chromosomes, and for those who are unable to make normal sperm for some other reason, he says.

However, it would probably be impossible to fertilize a human egg by using just these same two genes; researchers still have much work to do to define which genes from the human Y chromosome would be minimally essential to give rise to healthy offspring.

In the future, it may be possible to bypass the Y chromosome altogether, says Ward. She is working to find genes on other chromosomes that interact with Y chromosome genes; activating these partner genes might completely eliminate the need for the original Y chromosome genes, she says.

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Corrections

Corrected: A previous version of this article said “The same team had previously reported that male mice missing only seven genes from their Y chromosomes could father healthy babies.” The correct statement is that mice *with* only seven such genes could be fathers.

References

1. Yamauchi, Y. *et al*. *Biol. Reprod.* **81**, 353–361 (2009).
2. Yamauchi, Y., Riel, J. M., Stoytcheva, Z. & Ward, M. A. *Science* http://dx.doi.org/10.1126/science.1242544 (2013).