It Takes Two

Two genes from the Y chromosome are sufficient to generate male mice capable of fathering healthy offspring via an assisted reproductive technique.

By Jef Akst | November 21, 2013

A healthy and fertile daughter of a Y-less male, shown with her own litter
MONIKA WARD

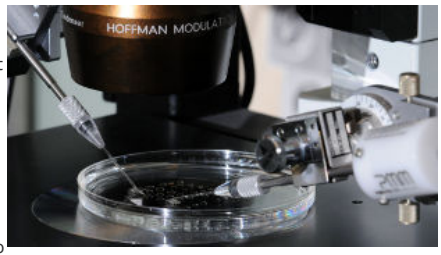
Sry, long known to be critical for the development of testes, and *Eif2s3y*, more recently recognized as the kick-starter of spermatogenesis, are all the only genes from the Y chromosome required for male mice to generate early-stage sperm precursors capable of fertilizing eggs and yielding live offspring, according to new research published today (November 21) in *Science*.

"It's quite an amazing technique to be able to get live, healthy offspring from round spermatids, which are way early in the final process of sperm maturation," said Polly Campbell, an evolutionary biologist who studies the genetics of speciation at Oklahoma State University but was not involved in the research. Moreover, she added, the spermatids often showed abnormal morphology, yet were still able to yield offspring through an assisted reproductive technique. "That is probably the single most striking thing about this paper," she said.

Reproductive biologist Monika Ward from the University of Hawaii in Honolulu has long been interested in the function of genes that exist on the male-only Y chromosome. Previously, Ward's group had shown that it was possible to generate live offspring from male mice lacking the entire long arm of the chromosome, narrowing the search for the bare minimum Y genes required for the development of workable gametes to the short arm, which contains just seven genes and three gene families. Recognizing that the animals would be unable to make any sperm-like cell without testes, Ward and her colleagues figured that *Sry* was probably essential. And research from other groups had suggested that another gene, *Eif2s3y*, was key to initiating spermatogenesis. Indeed, earlier reports had suggested that male mice lacking the Y chromosome but carrying *Eif2s3y* generated some amount of sperm precursor cells known as round spermatids.

So Ward's group set out to confirm that mice carrying these two genes but lacking the rest of the Y chromosome would produce these round spermatids, and to see whether the cells could be used to produce live offspring. Sure enough, though the testes of these Y-less males were smaller than those of wild-type males, they did contain some germ cells. Plating these cells, Ward and her colleagues were able to identify some round spermatids. They were rare, many were abnormally shaped, and some were still diploid, having not successfully completed the second round of meiosis required for the formation of haploid gametes, but they were there. The researchers isolated these spermatids and injected them into healthy female mouse eggs using a technique known as round spermatid injection (ROSI). The next day, they saw signs of fertilization, and transplanted the embryos into the oviducts of recipient females, who went on to deliver live, healthy offspring. Notably, however, the procedure had a fairly low success rate of only 9 percent, compared with a 26 percent success rate of ROSI with spermatids from wild-type males.

"It's a very interesting piece of science, which says that the bare minimum to get offspring is *Sry* to make a testis and [*Eif2s3y*] to allow spermatogenesis to proceed in some cells to the point where you can use them to fertilize an egg, but you have to use propagated methods to do so and it's not very efficient," MRC National Institute for Medical Research's Robin Lovell-Badge, a geneticist and stem cell biologist in field of sex determination who was not involved in the present study.



The micromanipulation setup, in which oocytes are injected with round spermatids to achieve fertilization from males lacking a Y chromosome
MONIKA WARD

Moreover, the ability to use assisted reproductive technologies to generate live offspring from males containing just these two genes does not mean that the rest of the Y isn't important, Ward noted. The other genes are undoubtedly important for the completion of sperm development and normal fertilization, enabling males to successfully reproduce without assistance. Indeed, when the researchers added in three additional Y genes, as well as a partial chromosome to pair with the partner-less X during cell division, they were able to achieve success rates as high as 20 percent. "For normal male fertility, other genes on the Y are absolutely important," Campbell said. Identifying which gene is responsible for this bump, as well as what each of the Y-chromosome genes does, is a continued goal of Ward's research.

In addition to probing Y gene functions, Ward also hopes that her team's work will prompt a reexamination of ROSI as a possible technique for addressing male infertility in humans. While ROSI has reportedly supported the birth of healthy children, it is considered an experimental technique that is not

widely used due to safety concerns and technical hurdles. "I hope that our work maybe will incite basic scientists and clinicians to study the round spermatid injection a little bit more, with the hope that one day in the future this method will become acceptable and will enable this special group of infertile men to father children," said Ward.

Y. Yamauchi et al., "Two Y genes can replace the entire Y chromosome for assisted reproduction in the mouse," *Science*, 10.1126/science.1242544, 2013.

Tags

Y chromosome, sex differences, sex determination, male infertility, genomics, genetics & genomics, evolutionary biology and evolution

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A 9% success rate? I know that there are a few grad students out there that deserve an extra special thank you, and probably a hug after the amount of work it took to make this awesome paper!

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