New technique overcomes genetic cause of infertility

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Graphical depiction of XXY chromosomes. Credit: Joe Brock

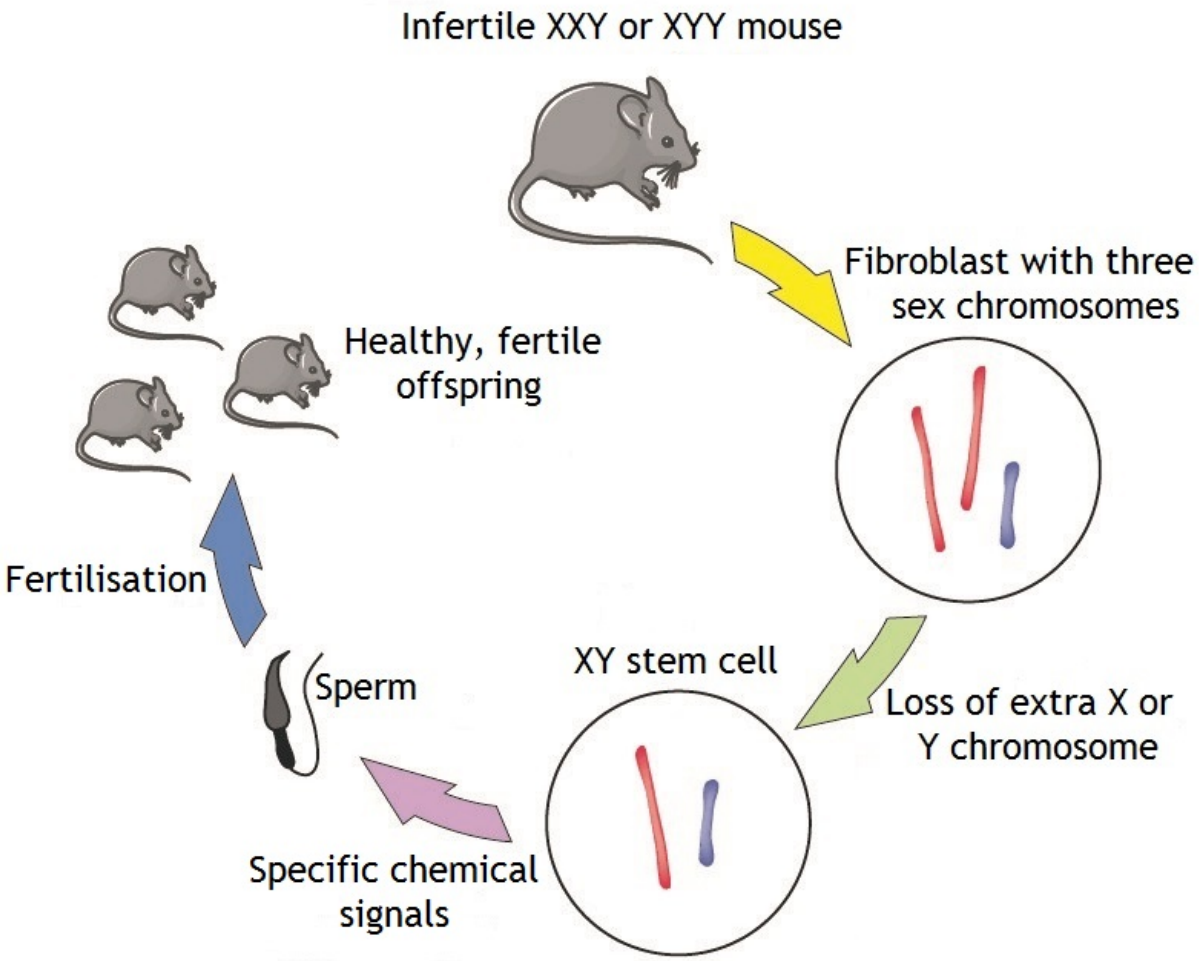
Scientists have created healthy offspring from genetically infertile male mice, offering a potential new approach to tackling a common genetic cause of human infertility.

Our sex is determined by the X and Y chromosomes. Usually, girls have two X chromosomes (XX) and boys have one X and one Y (XY), but approximately 1 in 500 boys are born with an extra X or Y. Having three rather than two sex chromosomes can disrupt formation of mature sperm and cause infertility.

In a new study published in *Science*, scientists at the Francis Crick Institute have found a way to remove the extra sex chromosome to produce fertile offspring. If the findings can be safely transferred into humans, it might eventually be possible for men with Klinefelter syndrome (XXY) or Double Y syndrome (XYY) that are infertile to have children through assisted reproduction using this technique.

The research was done in collaboration with Kyoto University and funded by the European Research Council, the Japan Science and Technology Agency, and the Japan Society for the Promotion of Science.

The team took small pieces of ear tissue from XXY and XYY mice, cultured them, and collected connective tissue cells known as fibroblasts. They turned the fibroblasts into stem cells and noticed that in the process, some of the cells lost the extra sex chromosome. With an existing method, they used specific chemical signals to 'guide' the stem cells into becoming cells that have the potential to become sperm. These cells developed into mature sperm when injected into the testes of a host mouse. The researchers then harvested these mature sperm and used them through assisted reproduction to create healthy, fertile offspring.



Research schematic. Credit: Takayuki Hirota

"Our approach allowed us to create offspring from sterile XXY and XYY mice," says first author Takayuki Hirota from the Francis Crick Institute. "It would be interesting to see whether the same approach could one day be used as a fertility treatment for men with three sex chromosomes."

In a preliminary experiment, the team found that stem cells produced from fibroblasts of men with Klinefelter syndrome also lost the extra sex

chromosome.

However, lots more research is needed before this approach could ever be used in humans. Senior author James Turner, Group Leader at the Francis Crick Institute, explains: "There is currently no way to make mature sperm outside of the body. In our mouse experiments we have to inject cells that have the potential to become sperm back into the testes to help them finish developing. But we found that this caused tumours in some of the mouse recipients. So reducing the risk of tumour formation or discovering a way to produce mature sperm in a test tube will have to be developed before we can even consider this in humans."

More information: T. Hirota el al., "Fertile offspring from sterile sex chromosome trisomic mice," *Science* (2017). science.sciencemag.org/lookup/ … 1126/science.aam9046

Provided by The Francis Crick Institute