Genetics discovery sheds new light on function of Y chromosome gene

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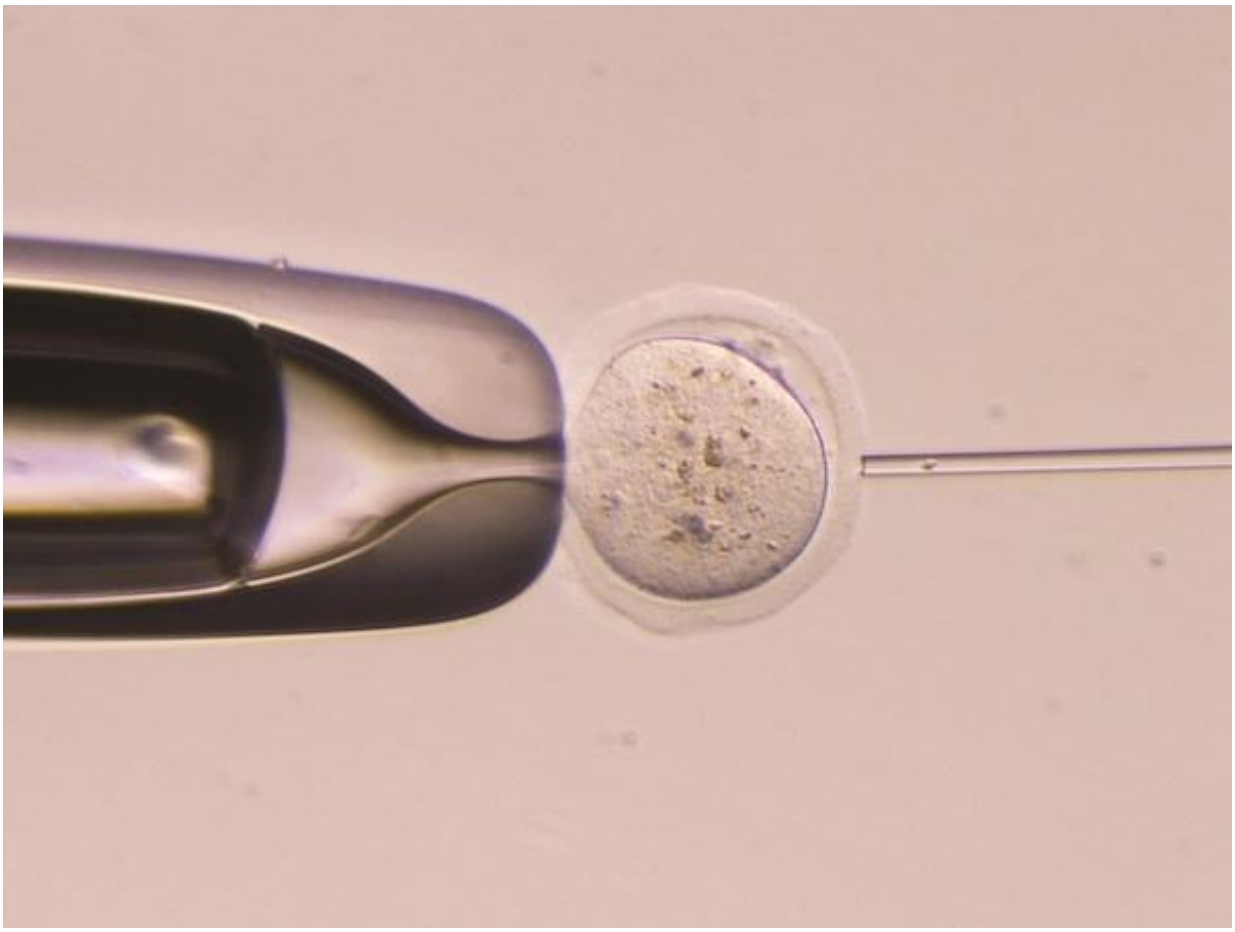
Dr. Monika Ward in her lab at the Institute for Biogenesis Research.

Scientists from UH Mānoa have uncovered substantial new knowledge about the function of the Y chromosome gene.

The researchers, including Dr. Monika Ward, post-doctoral fellows Yasuhiro Yamauchi and Jonathan Riel, and PhD student Victor Ruthig, who are all from of the Institute for Biogenesis Research (IBR), have discovered that only three genes from the Y chromosome are needed for male mice to make sperm able to fertilize oocytes and generate offspring after Intracytoplasmic Sperm Injection (ICSI), a fertilization technique developed at the John A. Burns School of Medicine at UH Mānoa.

Two years ago the same group reported it successfully obtained offspring from male mice that had only two Y chromosome genes, testis determinant Sry and spermatogonial proliferation factor Eif2s3y. These males did not produce sperm and, to achieve fertilization, researchers had to use the immature precursor cells, spermatids, and a technique called Round Spermatid Injection (ROSI). The Practice Committee of the American Society of Reproductive Medicine and the Practice Committee of the Society for Assisted Reproductive Technology considers ROSI an experimental procedure and do not recommend it for treatment of male infertility. ICSI, however, is used commonly worldwide, with thousands of children born annually.



ICSI, developed at the IBR, is used around the world for in vitro fertilization.

At the IBR, researchers considered which of the Y chromosome genes may be responsible for turning spermatids into sperm. In an international collaboration with Paul Burgoyne's group from Francis Crick Institute in London, England, and Michael Mitchell from INSERM, in Marseille, France, they hypothesized that the key gene is Zfy2 (zinc finger protein 2). They added the Zfy2 transgene to males already transgenic Sry and Eif2s3y and lacking the Y chromosome. The resulting males carrying only three Y chromosome genes were producing sperm. These males were not able to reproduce on their own because their sperm number was

too low. But when the researchers harvested sperm from the testes and injected them into the oocytes, they become fertilized. And when the embryos were transplanted to surrogate mothers, young were born with the same efficiency as from males with normal intact Y chromosome.

Demonstration that three Y chromosome derived genes are enough for a formation of sperm functional in assisted fertilization is an important finding advancing current knowledge about Y chromosome gene function

"Considering that ICSI, and not ROSI, is commonly used in human infertility treatment, the findings bear translational significance," said Dr. Ward. "Transformation of round spermatids into sperm is a key developmental process gaining a lot of attention due to newly ascribed roles for the sperm epigenome in fertilization and transgenerational inheritance." Dr. Ward's study points to Zfy2 being a key regulator in this process, including the function of its end product—spermatozoa.

Dr. Ward's team described the discovery in a manuscript published by the leading genetics journal *PLoS Genetics*. An accompanying manuscript from Burgoyne and Mitchell groups will appear in *PLoS One*.

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