Researchers find gene mutation that causes infertility in male mice

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Up to 15 percent of couples of childbearing age struggle with the heartache of infertility. Now there is the promise of new hope with Cornell researchers' identification of a mutation in a gene that causes male infertility in mice. Because this is the first time that a dominant mutation that leads specifically to infertility in a mammal has been discovered, the researchers say they can now look for similar mutations in the DNA of infertile men.

"If you consider infertility a disease, you can't study it like you would other diseases, because the affected people can't reproduce," said John Schimenti, director of Cornell's Center for Vertebrate Genomics and senior author of the paper published in the current issue of the Public Library of Science journal *PLoS Biology*. Laura Bannister, a research associate in Schimenti's laboratory, is the paper's lead author.

"Consequently, we know very little about the genetic causes of infertility in humans," said Schimenti, a Cornell professor of genetics.

The gene, called Dmc1, provides the code for a key protein involved in meiosis, the process that produces sperm and egg cells for reproduction. These sex cells contain only one set of chromosomes that combine during conception and create an embryonic cell with two chromosome sets, one from each parent.

The mutation leads to a change in an amino acid in Dmc1 that blocks meiosis in its tracks, preventing sperm production. The mutant allele

(one version of the pair of genes we inherit from each parent) is dominant; females who carry it remain fertile but carry the defect and pass the mutation on to future generations.

However, female carriers show higher rates of abnormalities during meiosis, which can potentially cause chromosome imbalances and birth defects, the researchers discovered. In addition, the researchers found that female mice with the Dmc1 mutation are born with fewer egg cells and can run out of eggs prematurely -- resulting in early menopause (or "mousapause" as the researchers humorously refer to the condition).

To get their results, the researchers randomly induced mutations in the mouse genome and then looked for infertility in the resulting mice. They then analyzed the DNA of the sterile males and identified the allele that caused the infertility. While most studies on the genetics of fertility stem from analyses of mice that have had a custom gene "knockout," this is the first to reveal a dominant mutation that leads specifically to infertility in a mammal. The researchers believe this kind of dominant effect is closer to how real-life infertility occurs in humans.

"People have been sequencing genes in humans, including the Dmc1 gene, to try and associate changes in gene sequences with infertility," said Schimenti. "There have been occasional reports that in some patients, a sequence change in this or other meiosis genes might cause a dominant defect in function, but until now there has been no definitive proof."

Mouse models, he said, will be critical in distinguishing between those DNA sequence changes that are benign in humans versus those that disrupt sperm or egg production. The researchers are engaged in a project to identify ultimately all the genes needed for fertility in mice and apply this information to the human situation.

Source: Cornell University