

## Gene discovery could lead to male contraceptive

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Mouse studies have shown that the CATSPER1 gene is present in sperm and is essential for normal sperm motion during fertilization. The left side of the diagram illustrates normal sperm fertilizing an egg. The right side of the diagram illustrates that sperm lacking the CatSper1 protein are not able to penetrate an outer layer of the egg, known as the zona pellucida, preventing normal fertilization. Credit: University of Iowa. Image adapted from Avenarius et al 2009 AJHG in press.

A newly discovered genetic abnormality that appears to prevent some men from conceiving children could be the key for developing a male contraceptive, according to University of Iowa researchers reporting their findings in the April 2 online edition of the *American Journal of Human Genetics*.

Although female oral contraceptives were developed over 40 years ago and have proven very effective for family planning, no similar pharmacological contraceptive has been developed for males. Surveys conducted by the Medical Research Council Reproductive Biology Unit in the United Kingdom, suggest that men would be willing to use a



pharmacological contraceptive if one was available. Presently the only contraceptives available for men are condoms or a vasectomy.

"We have identified CATSPER1 as a gene that is involved in nonsyndromic male infertility in humans, a finding which could lead to future infertility therapies that replace the gene or the protein. But, perhaps even more importantly, this finding could have implications for male contraception," said Michael Hildebrand, Ph.D., co-lead author of the study and a UI postdoctoral researcher in otolaryngology at the UI Roy J. and Lucille A. Carver College of Medicine.

The research team, which included scientists from the University of Social Welfare and Rehabilitation Sciences in Tehran, Iran, discovered the male infertility gene while studying the genetics of families from Iran -- a population that has relatively high rates of disease-causing gene mutations.

Although the team's research with these Iranian families focuses on identifying genetic causes of deafness, collecting genetic information from this population allowed the researchers to identify two families where male infertility that was not part of a syndrome appeared to be inherited. The affected men's infertility was diagnosed with a routine semen analysis.

Focusing on a group of <u>genes</u> that have been implicated in male infertility in mice, the researchers found that mutations in both Iranian families occurred in a single gene called CATSPER1. DNA analysis revealed two different mutations -- one in each family -- but both mutations would likely lead to either a very truncated, non-functional version of the protein, or no protein at all. Neither mutation was found in the DNA of 576 Iranian individuals who were screened as controls.

Harvard University studies on mouse models that lack the CATSPER1



gene reveal how sperm is affected when the protein is missing or abnormal. These studies show that CATSPER1 mutations affect sperm motility, specifically the very vigorous hyperactive motion the sperm uses when it is entering the egg during fertilization.

"Our research suggests that the defect in sperm hyperactivity that is seen in mice without CATSPER1 will also occur in humans with the genetic mutation," Hildebrand said. "Identification of targets such as the CATSPER1 gene that are involved in the fertility process and are specific for sperm -- potentially minimizing side effects of a drug targeting the protein's function -- provide new targets for a pharmacological male contraceptive."

Several approaches to male contraception are currently under investigation at other institutions. One approach that could potentially target CATSPER1 is immunocontraception where antibodies are developed that bind to a targeted protein and block its function. Immunocontraception is still in early stages of development and in order to be useful it will need to be proven effective, safe and reversible.

Source: University of Iowa (<u>news</u> : <u>web</u>)

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