

# Penn Vet Team Identifies a Gene Responsible for Male Infertility and a Respiratory Disorder

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A team of researchers from Penn Vet has characterized a protein responsible for sperm tail formation that, when missing, causes male infertility, brain abnormalities and other problems in mice.

Jeremy Wang, PhD, associate professor of developmental biology and director of the Center for Animal Transgenesis and Germ Cell Research at Penn Vet, led the study, collaborating with postdoctoral researcher Jian Zhou and research specialists Fang Yang and Adrian Leu.

The work, published in the journal *PLoS Genetics*, has implications for providing genetic counseling and in vitro fertilization to men with certain infertility problems, as well as to the one in 16,000 people who suffer from a condition known as Kartagener syndrome, or primary ciliary dyskinesia.

Some men with infertility have sperm that cannot swim properly. One of the causes of this immobility may be a disruption in the function of cilia, hair-like structures that help cells move themselves or other objects around. The root cause of primary ciliary dyskinesia, or PCD, also appears to be a defect in cilia function.

Delving into the complex structure of cilia, the Penn researchers examined a protein called MNS1 or meiosis-specific nuclear structural protein 1, which they found located in the sperm tail.

To get at the function of MNS1, the team created mice bred to lack the protein. Though the mutant mice grew normally, fewer were born than expected, indicating that the mutation might be lethal in some embryos or very young mice.

In addition, Dr. Wang said, “the mutation has a very interesting phenotype.”

Male mice that lacked MNS1 were sterile. Their sperm count was only 8 percent of that seen in normal mice, and the vast majority of sperm present had very short tails, impairing their ability to swim. The fact that the sperm had normal heads but malformed tails also indicated to the scientist that the MNS1 mutation affected formation of the sperm tail, which is a specialized type of cilium.

In working with the mutant mice, the researchers noticed that more than half bore another unusual trait: some or all of their internal organs were reversed in position, the heart on the right instead of the left and so on. This condition, known medically as situs inversus, is also seen in about half of PCD patients. The patterning and formation of internal organs is another process that is dependent in part on cilia.

With growing evidence that MNS1 played a role in cilia function, the researchers looked to other parts of the body where cilia are vital, including the brain, where cilia direct cerebrospinal fluid, and the trachea, where cilia help move fluid and mucous.

They found that the mutant mice developed hydrocephalus, or a swelled head, consistent with a lack of cilia function. And upon examining cilia in the trachea, they found abnormalities. In the MNS1-deficient mice, the cilia had only about half the normal number of dynein arms, structures that provide the power for cilia to move.

Dr. Wang and colleagues are now working to determine the mechanism by which MNS1 affects cilia function.

“We still don’t really understand how this protein works,” Dr. Wang said. “We’re trying to characterize a number of proteins that potentially interact with MNS1.”

They’re also planning to partner with in vitro fertilization clinics to screen infertile males for deficiencies in the MNS1 gene. If it turns out that some of these men have a mutation that renders MNS1 nonfunctional, Wang said, “they won’t be able to conceive naturally, but, in the clinic, technicians can just inject the sperm head into the egg and achieve fertilization.”

In addition, if scientists confirm that mutations in MNS1 are responsible for some of the effects of PCD, in the future the syndrome could potentially be treated with gene therapy, which has shown promise in ameliorating certain respiratory conditions.

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