

# Gene defects could be new cause of male infertility

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Scientists at the University of North Carolina at Chapel Hill have identified a gene crucial to the final step of the formation of a functional sperm cell.

That final step – called spermiogenesis – entails the compaction of DNA into a tight ball within the head of the sperm so it can successfully penetrate an egg.

Mice engineered to lack the crucial gene, *Jhdm2a*, that triggers this process did not produce many mature sperm, and those they did produce had abnormally shaped heads and immotile tails.

“Defects in this gene could be the cause for some cases of male infertility,” said study senior author Yi Zhang, Ph.D., Howard Hughes Medical Institute investigator and professor of biochemistry and biophysics in the UNC School of Medicine. Zhang is also a member of the UNC Lineberger Comprehensive Cancer Center.

“Because this gene has a very specific effect on the development of functional sperm, it holds great potential as a target for new infertility treatments that are unlikely to disrupt other functions within the body.”

The study, published on-line in the journal *Nature* Wednesday (Oct. 17, 2007), provides evidence that *Jhdm2a* directly controls expression of several genes required for DNA packaging in sperm cells. The research was funded by the Howard Hughes Medical Institute and the National

Institutes of Health. For a sperm cell to mature fully, multiple molecular events have to occur, such as assembly of a sperm tail and packaging of sperm DNA.

In the sperm cell, yarn-like strands of DNA wrap around spools of protein called histones that package the DNA so it fits into the nucleus. Chemical tags such as methyl groups affixed to the histones govern how tightly the DNA can be packaged, affecting the accessibility for the gene to be switched on or off.

Previous studies have shown that when a gene is turned off, one of these histones, H3K9, carries a methyl tag. In a study published in *Cell* last year, Zhang's laboratory demonstrated that the enzyme Jhdm2a removes this methyl tag, allowing the gene to become switched on, or expressed.

“Although a number of histone demethylases have been identified, very little is known regarding their biological functions, particularly in the context of whole animals,” said Yuki Okada, Ph.D., a postdoctoral fellow in Zhang's laboratory and lead author on the study.

The unique expression pattern of Jhdm2a suggests that this demethylase may play an important role in the late stages of sperm cell development. In this study, mice genetically engineered to lack this gene had smaller testes, a significantly lower sperm count, and were infertile.

In addition, the few sperm that were produced by these mutant mice displayed significant morphological defects, including abnormally shaped heads and immotile tails.

To assess the packaging state of the sperm DNA, the researchers used electron microscopy and a fluorescent dye called acridine orange, which fluoresces differently depending on the packaging state of a sperm. Both techniques revealed a defect in sperm DNA packaging in the mutant

mice, suggesting that incomplete DNA packaging was the cause of infertility.

“There are several mouse models that exhibit the male infertility seen in human syndromes such as azoospermia (absence of sperm) or globozoospermia (sperm with round heads),” said Zhang, “However, most of the genes required for normal spermatogenesis in mice are intact in human patients, raising the possibility that we might consider the *jhdm2a* gene as a culprit in these human male infertility syndromes.”

Zhang and his colleagues are now looking for mutations in this gene in infertility patients, and are also interested in identifying the partners or cofactors in the cell that help this gene do its job.

Source: University of North Carolina at Chapel Hill

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