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RESEARCH NEWS

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Mutation on Y Chromosome Stops Sperm Production

After an arduous search, Howard Hughes Medical Institute (HHMI) investigator David Page has found the first mutation on the Y chromosome that prevents sperm production and thus causes male infertility. The finding, described in the December issue of the journal *Nature Genetics,* may eventually help in the design of male contraceptives and treatments for infertile males.

"It's been very difficult to find the smoking gunthe definitive evidence that any particular gene is the cause of male infertility," said Page, whose laboratory is at the Whitehead Institute for Biomedical Research at the Massachusetts Institute of Technology. "Of course this is only one case so we have certainly not solved a public health problem. But at least it's a first instance where we can provide an explanation."

Researchers have uncovered the genetic causes for a flood of diseases as more DNA data have become available. But the study of infertility has lagged. "The very idea that infertility could be genetic seemed not all that logical," said Page. "Most people didn't get beyond the idea of what genetics isthe study of disease passed on in familiesand the definition of infertilitythe inability to have families."

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Genetics and infertility can coexist, however. The impact of an infertility mutation can be hidden, for example, depending on the identity of other genes present in an individual. Thus it is important to see if signs of male infertility, such as a low sperm count, coincide in related individuals such as brothers and uncles.

For now only about 20 percent of cases of male infertility can be traced either to the loss of a large chunk of the male Y chromosome, or to some other large chromosome abnormality, such as the presence of a second X chromosomes in a male. Normal males have an X and a Y chromosome, whereas females have two X chromosomes.

Page wanted to see which gene within one of the large missing Y chromosome chunks was important. He first determined the entire DNA sequence for a region of the Y chromosome that is missing in a number of infertile males. He found that the region contained only two genes, so he set out to test the DNA sequence of the genes in 576 infertile males.

One of the genes, named *USP9Y*, contained variant DNA sequences in the samples from five of the infertile males. Four of the changes were harmless red herringsthey were also present in a fertile brother or father or caused no change in the final protein product from the gene. But the change in one individual, code-named WHT2780, was not present in the individual's fertile brother, even though the two brothers had inherited the same Y chromosome from their father.

"The mutation must have appeared for the first time in WHT2780, and thus is an excellent candidate for causing his infertility," explained Page.

WHT2780 does not produce any sperm, but he does produce a messy mixture of sperm-precursor cells. Sperm cells normally pass through these precursor stages over a period of 65 days, as they move through the convoluted seminiferous tubules that wind through the testes.

"I expected that these mutations would cause interruptions at discrete points in the 65-day process," said Page. "In a typical infertile male the problem is a reduction in the overall volume of sperm production."

Some tubules appear to function appropriately, while others do not function at all. "It's as if the lights are going out one by one," said Page. "It makes me wonder whether the key to many of the problems will go back to the germ stem cellsthe original sperm progenitor cellswhose job it is to keep the tubules populated with sperm-producing cells."

To see if that speculation is a reality, Page needs to determine *USP9Y's* function and identify more genes that cause male infertility. The latter task will not be easy, as some genes on the Y chromosome come in multiple similar versions that confuse analysis, but Page's job will be made easier by the determination of the complete sequence of the Y chromosome. Page and his colleagues expect to have the finished blueprint for the Y chromosome by the end of the year 2000.

A better understanding of how mutation causes infertility could suggest how to create infertility at will. A drug that antagonizes a gene such as *USP9Y* has

the potential to be a male contraceptive.

Then there is the even more challenging prospect of correcting mutations that cause infertility. "There may be public health jackpots to be found," said Page. "It's going to be a challenge to find them, but they're probably out there."