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Fathers Pass Infertility to Sons

Researchers have discovered that sons conceived with the aid of a popular *in vitro* fertilization technique can inherit the same genetic defects that rendered their fathers infertile.

HHMI investigator David Page of the Whitehead Institute for Biomedical Research at Massachusetts Institute of Technology and his colleagues studied three men who fathered sons through a widely used fertilization technique called intracytoplasmic sperm injection (ICSI). In each case, the fathers passed on a Y chromosome genetic defect called an AZFc deletion. Such deletions are the most frequent molecularly defined cause of failure to produce sperm, affecting about five to ten percent of infertile men with insufficient sperm production. The research was published in the July issue of the journal *Human Reproduction*.

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— David C. Page

Page also noted that researchers in Taiwan published an article in the June issue of the journal *Fertility and Sterility* that describes another family in which a son conceived by ICSI inherited the AZFc defect from his father.

In treating AZFc-deficient men with ICSI, clinicians isolate the few sperm that are produced and inject a single sperm directly into an egg. The fertilized egg is then implanted in the mother.

While fertility experts had strongly suspected that the AZFc deletion could be inherited in such cases, that suspicion had not been clinically confirmed until now. The finding raises thorny ethical questions about assisted reproduction techniques. "I think this finding is going to change genetic counseling," said Page, "because what had been a theoretical concern is now concrete. Now we have four families, including the one in Taiwan, in which there are boys who in all likelihood will be infertile as adults." (Girls are unaffected by the defect, since they receive an X chromosome, rather than the defective Y chromosome, from their fathers.)

Despite knowing about the defect and its inheritance pattern, couples might not be deterred from trying to have sons, said Page.

"I am told by clinicians with whom I collaborate that most of the couples they treat would simply wish to go ahead with having children via ICSI. Some, in contrast, might elect to avoid transmitting the infertility by using donor sperm or by adopting, and others could decide to have only daughters by genetically testing the fertilized embryos to determine their sex and only having female embryos implanted," said Page.

Page cautioned that genetic engineering of sperm to correct the defect is still a farfetched notion "because, of course, any such attempt at gene repair would carry with it the potential for collateral damage."

A more likely remedy, says Page, is the possibility that affected males, who may produce normal amounts of sperm during puberty and young adulthood, may decide to have their sperm harvested for future use. To date, however, scientists have not conducted careful clinical studies to explore the link between changing sperm counts and age, he said.

"We only know now that men in their twenties and thirties with AZFc deletions can have considerable variability in the number of sperm in their semen." If sperm counts do prove to be higher in younger affected males, said Page, they might have their sperm harvested and stored until they are ready to start a family.

The latest findings emphasize the importance of basic research in understanding the mechanisms by which Y chromosome deletions cause infertility, said Page. "We really don't know why this missing piece of the Y chromosome leads to spermatogenic failure, but we are learning more and more about the missing genes," he said.