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Searching the Y chromosome for a "house with green shutters"

A team of U.S. and Finnish scientists has found that a specific defect in the Y chromosome may be responsible for 13 percent of cases of azoospermia, the inability to make sperm and the most severe form of male infertility.

This study is one of the first to demonstrate that genetic defects can sometimes explain infertility in otherwise healthy couples and could lead to a better understanding of the molecular mechanisms required to make healthy sperm. The research, reported in the August issue of *Nature Genetics*, was led by David Page, an HHMI investigator at the Whitehead Institute for Biomedical Research.

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The researchers examined the Y chromosome of 89 men with azoospermia and found that 12 of the men were missing a tiny fragment of the chromosome's long arm. These men were otherwise healthy and showed no signs of physical obstruction in their reproductive tract. The fathers of the men had Y chromosomes intact in this region as did 90 fertile men studied for comparison. Based on these observations, Page and his colleagues concluded that azoospermia resulted from a newly arising mutation in the Y chromosome and that a gene (or genes) located in the missing region is required for sperm production.

"Despite medical advances in treatment, there are many couples who never learn the cause of their infertility," said Page, who also led the team that completed the first comprehensive map of the Y chromosome in 1992. "Little attention has been paid to the possibility that fertility problems can have a genetic basis. Our findings will help some couples get a definitive answer about the reasons for their infertility and may eventually lead to new directions in infertility therapy."

In this study, the HHMI scientists meticulously combed the Y chromosomes of the infertile men for missing DNA landmarks, using the 1992 physical map of the Y chromosome as a guide. When they found that a significant number of infertile men were missing a common region, they began to scrutinize that region. So far, the team has found a single gene, DAZ (deleted in azoospermia), in the common deleted region. Page said, however, that they don't yet know if this gene is the long-sought azoospermic factor required to make sperm. Scientists have suspected that the Y chromosome carries such an azoospermic factor, but the precise molecular identity of that factor remains unknown.

The Y chromosome map helped Page and his colleagues narrow the search for the gene to a small region on the chromosome. "Finding the DAZ gene within this region is the equivalent of locating a friend's house when you know it has green shutters and stands within one city block of an important landmark," Page said. "The DAZ gene appears to be a reasonable candidate for the azoospermic factor, but more studies will be required to determine whether it is the only house on the block with green shutters. There may be others that we haven't seen yet."

Infertility affects nearly 10 percent of all Americans, and each year as many as 20,000 couples undergo *in vitro* fertilization in the hope of conceiving. The causes of infertility range from physical abnormalities in the male or female reproductive tracts to lingering effects of bacterial and viral infections. Two percent of all males, however, have no such abnormalities and are otherwise healthy except that they do not produce new sperm (azoospermia) or they produce only few or deformed sperm (oligospermia).

The HHMI team, together with Sherman Silber of St. Luke's Hospital in St. Louis, Mo., also studied biopsies of the testes of the men with the Y deletion. Their studies revealed that although none of the men produced mature sperm, some were capable of making immature sperm cells. In addition, the biopsies showed surprisingly variable testicular manifestations, even with similar deletions; what had been viewed as distinct clinical disorders may actually have a common cause.