WHITEHEAD INSTITUTE

STUDY PAINTS NEW PICTURE OF Y CHROMOSOME AS A SAFE HAVEN FOR MALE FERTILITY GENES

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CAMBRIDGE, Mass. — For decades scientists thought that the human Y chromosome, the male sex chromosome, was nothing more than a smaller, less stable version of its partner, the X (the sex chromosome present in both females and males). However, new research led by Dr. David Page, member of the Whitehead Institute for Biomedical Research, and associate investigator of the Howard Hughes Medical Institute, reverses this unflattering picture of the Y and reveals it as a crucial player in the evolution of sex chromosomes and also as a safe haven for male fertility genes.

These results are not only generating a new respect for the Y chromosome but also could lead to novel diagnostic techniques for thousands of infertile men. The results also have profound implications for understanding the genetic differences between men and women and the genetic underpinnings of chromosomal disorders such as Turner syndrome.

In the October 24 issue of Science, Dr. Page and first author Dr. Bruce Lahn report that a systematic search of the Y chromosome yielded 12 novel genes in the non-recombining region of the Y (NRY)—a region of the Y, that unlike other chromosomes, does not undergo recombination, or exchange genetic material with its partner, the X. Along with eight previously identified genes, the 12 novel genes compose a substantial, nearly comprehensive catalog of genes found in the NRY (which constitutes 95 percent of the Y chromosome). The scientists found that the 12 genes they discovered could readily be sorted into two categories. Genes in the first group are expressed in many organs, are copies of genes found in the X, and perform housekeeping functions. The second group consisted of genes that are expressed only in the testes, are exclusive to the Y, and probably are responsible for enhancing male fertility.

"These results show that the Y chromosome is functionally coherent; it has a short list of missions to which it is dedicated. By contrast, other human chromosomes contain motley assortments of genes with no theme or unifying purpose apparent. The human Y chromosome is a striking exception," says Dr. Page.

NEW PICTURE OF Y

"As recently as ten years ago, many biologists assumed that the Y chromosome was a genetic wasteland except for one important gene, the sex-determining gene, " says Dr. Page. "Even when we and others did find other genes on the Y, they generally turned out to be copies of genes found on the X, which only supported the wasteland model of the Y chromosome."

Although these notions started to change when Dr. Page and others began discovering the genes related to male fertility on the Y, scientists continued to regard the rest of the Y chromosome as functionally inert. So Drs. Page and Lahn conducted a systematic search for a broad, representative sampling of genes on the Y to help form meaningful generalizations about the NRY's gene content.

Of the 12 genes they found, five were copies of genes found on the X. Termed the X-homologous genes, these genes occurred in a single copy. The other seven genes, specifically expressed only in the testes and exclusive to the Y, seem to occur in multiple copies on the NRY. Scientists also found that six of the eight previously discovered Y chromosome genes also fit into one or the other of these two categories.

Based on these findings and previous studies, Dr. Page and his colleagues speculate that the Y chromosome evolved using two strategies.

FIRST EVOLUTIONARY STRATEGY: IMPLICATIONS FOR TURNER SYNDROME

The first strategy was designed to ensure that both sexes have comparable access to housekeeping functions. However, this strategy seemed at odds with the general behavior of X-Y gene pairs during mammalian evolution.

"Both the X and the Y evolved from autosomes and, over time, although most ancestral gene functions were retained in the X chromosome, all except the housekeeping genes were discarded from the Y chromosome. This resulted in males having only one copy of many genes and females having two copies, an inequality that was dealt with by the process called X-inactivation—the silencing of one copy of the X in females."

The discovery of the X-homologous genes on the NRY along with previous studies suggests the importance in human evolution of an additional solution: preservation of homologous genes on both NRY and X with male and female cells expressing two copies of such genes. "If this were true, the copies of NRY genes in the X would have to escape inactivation," says Dr. Page. Drs. Page and Lahn found that this was indeed the case; the X-homologs of the NRY genes they discovered did escape X- inactivation.

The scientists also discovered that the genes common to the X and Y were functionally interchangeable. This finding has implications for Turner syndrome, a disorder in which females are born with only one X chromosome. Scientists speculate that Turner syndrome may be caused by inadequate expression of some X-Y common genes that escape X inactivation. "Given that several X-NRY genes appear to be involved in cellular housekeeping, we speculate that some Turner syndrome characteristics reflect inadequate expression of particular housekeeping functions," says

Dr. Page. The scientists suggest that X-homologous NRY genes be investigated as candidates for Turner syndrome.

SECOND EVOLUTIONARY STRATEGY: IMPLICATIONS FOR MALE INFERTILITY

Drs. Page and Lahn speculate that the second strategy that shaped the NRY's evolution was the acquisition of male fertility genes from autosomal (or non-sex) chromosomes. Earlier studies had suggested that this was the case. Two years ago Dr. Page and his associates and collaborators from St. Louis and Finland discovered an NRY gene cluster called DAZ, that when missing, is associated with infertility in otherwise healthy males. When the Page lab scientists closely examined DAZ they found that it has a homolog, or close genetic cousin, on human chromosome 3. Through careful analysis of the two human genes, as well as closely related genes in the fly and the mouse, Dr. Page and his collaborators determined that an ancestral autosomal gene gave rise to the Y-chromosomal DAZ genes sometime during human evolution, after the separation of primate and mouse lineages. This evidence represented the first time that a Y chromosome in any species has been shown to have acquired a fertility factor during evolution, independent of the X chromosome.

"Our current study suggests that the transfer of male fertility factors from autosomes to Y may be a recurrent theme in Y chromosome evolution," Dr. Page says. "We suspect that autosome-to-Y transfer may have provided a competitive advantage for males early in human evolution." The NRY is the only portion of the human genome that is present exclusively in one sex.

BACKGROUND ON MALE INFERTILITY

About one in six American couples is infertile, and each year as many as 20,000 couples seek assisted reproductive technologies to help them conceive. In a fifth of the infertile couples, a key factor is a defect in sperm production, which could result from a variety of causes, including infections and other illnesses. However, until recently, scientists paid little attention to the possibility that a genetic component might be responsible for infertility. The concept of genetic infertility seemed like an oxymoron, since genetic disorders usually are thought to run in families rather than preclude their occurrence.

The situation changed two years ago when Dr. Page and his colleagues used a comprehensive genetic map of the Y chromosome to identify the DAZ gene, that when missing, causes azoospermia, the inability to produce sperm and the most severe form of male infertility. Then last year, the Page lab found that this same Y chromosome defect also can cause the most common form of male infertilitylow sperm production, or oligospermia. This study definitively showed that genetic defects can cause low sperm counts in some males. In addition, the scientists made another startling discovery: the Y mutation also was present in the sperm of one oligospermic man they tested.

"Normally, these men would not be able to have children. However, the explosion of assisted reproductive technologies, and especially of intracytoplasmic sperm injection (ICSI) the now-popular technology of injecting a single sperm into an egg to circumvent low sperm countsis making it possible for these men and their wives to have biological children. This raises the possibility that such men will actually pass on their infertility to their sons," says Dr. Page. He and his colleagues recommended that infertile couples contemplating ICSI should be offered genetic counseling and the option of a DNA test for the mutation before they begin assisted reproductive procedures.

BACKGROUND ON TURNER SYNDROME

All human embryos inherit 23 pairs of chromosomes: one pair of sex chromosomes and 22 pairs of non-sex, or autosomal, chromosomes. Embryos that inherit two X chromosomes (one from each parent) develop into females. Embryos that inherit an X chromosome from their mother and a Y chromosome from their father develop into males. However, one in 5,000 females is born with only one X chromosome or with an intact X chromosome and half a Y chromosome. This disorder is called Turner syndrome and is characterized by short stature, infertility, and defects in multiple organs. Genetic analyses of Turner syndrome patients has led to the discovery of two genes, RPS4X and RPS4Y, which may be responsible for some of this syndrome. The Page lab's latest studies will help open new doors as scientists continue to explore the genetic underpinnings of the syndrome in an attempt to provide insights to better diagnosis and therapy.

The October 24 Science paper is titled "Functional Coherence of the Human Y Chromosome." The authors are Dr. Bruce Lahn and Dr. David Page, from the Whitehead Institute for Biomedical Research, Howard Hughes Medical Institute, and Massachusetts Institute of Technology. Work reported in this paper was supported by the National Institutes of Health.

Whitehead Institute is a world-renowned non-profit research institution dedicated to improving human health through basic biomedical research. Wholly independent in its governance, finances, and research programs, Whitehead shares a close affiliation with Massachusetts Institute of Technology through its faculty, who hold joint MIT appointments.

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