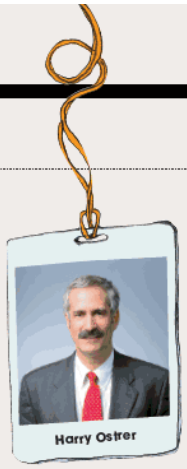
# Boy or Girl?

## A genetic switch for determining gender is found




A PERSON'S SEX, IT WOULD SEEM, is a matter of Xs and Ys: Through a biological twist of fate, each of us ends up either female, with two X chromosomes, or male, with one X and one Y. Yet sometimes a child is born with an X and a Y chromosome and develops physically as a female, and her brothers and male cousins may have underdeveloped or ambiguous genitalia.

A new study, led by Harry Ostrer, MD, professor of pediatrics, pathology, and medicine and director of the Human Genetics Program at NYU Langone Medical Center, describes a previously unidentified gene, MAP3K1, that may play a critical role in orchestrating human sexual development. The culmination of nine years of research, the findings, published recently in the *American Journal of Human Genetics*, could unlock the nuances of the genetic cascade that determines gender.

Since the discovery 20 years ago of a "maleness" gene, SRY, on the Y chromosome, a host of other gender-related genes have been found. MAP3K1, located on the fifth chromosome, represents a "new molecular switch," says Ostrer, which may "modulate the pathways between male and female development" and hold the key to understanding how these genes are connected.

This discovery, says Alexander Pearlman, PhD, a postdoctoral fellow at NYU Langone Medical Center and the first author of the study, addresses the delicate nature of human sexual development. Even though a person may have the genetic factors associated with being either male or female, he says, "a single base mutation could turn everything the other way."

Researchers unearthed this potent gene by examining individuals with disorders of sexual development (DSDs). These conditions, previously called intersex disorders, affect approximately 1 in 1,000 people and can cause numerous abnormalities.

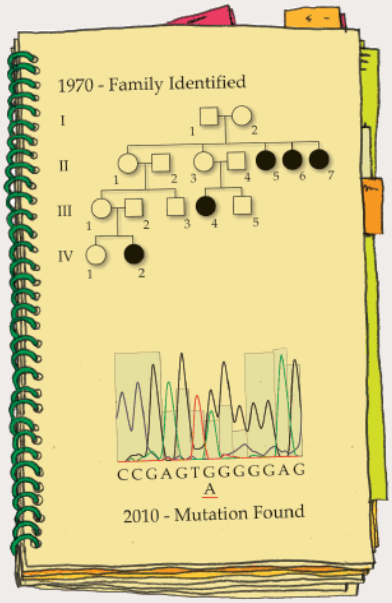
Dr. Ostrer's team studied one family from France, another from New Zealand, and several individuals with a condition known as 46,XY DSD. Though genetically male, some with the condition developed as females, and had partially developed ovaries, overdeveloped clitorises, or excessive hair, while others grew up as men and had urethral openings on the underside of their penises, small genitalia, or infertility. By carefully analyzing their DNA, Dr. Ostrer's team and collaborators from France, England, and Australia uncovered several mutations in the MAP3K1 gene and showed that they affected pathways favoring ovarian development.

Dr. Ostrer believes that the discovery will help scientists better understand normal development and provide an avenue for genetic screening, allowing clinicians "to explain a given condition, to identify other families who may be at risk, or to perform prenatal diagnosis." A new screening technique is already being used in France to identify affected individuals.

"Like it or not, biology is destiny," says Dr. Ostrer. These conditions "influence how people think about themselves and whether they consider themselves male or female." Better scientific understanding, he says, gives affected families peace of mind, providing them an explanation of the cause and helping clarify their options.

Dr. Ostrer plans to set up a national consortium to sequence the entire genome of affected individuals and their families, which he hopes will help researchers identify related genes and eventually develop new therapeutic options for those affected by these conditions. ●

*—JOSHUA FEBLOWITZ*




In 1970 a family with a condition known as 46,XY disorder of sex development was identified. By carefully analyzing the DNA of family members, the mutation responsible for the condition was recently discovered. This mutation results from the replacement of the base A (adenine) by G (guanine).

IMAGE COURTESTY OF HARRY OSTRER AND GORDON COOK