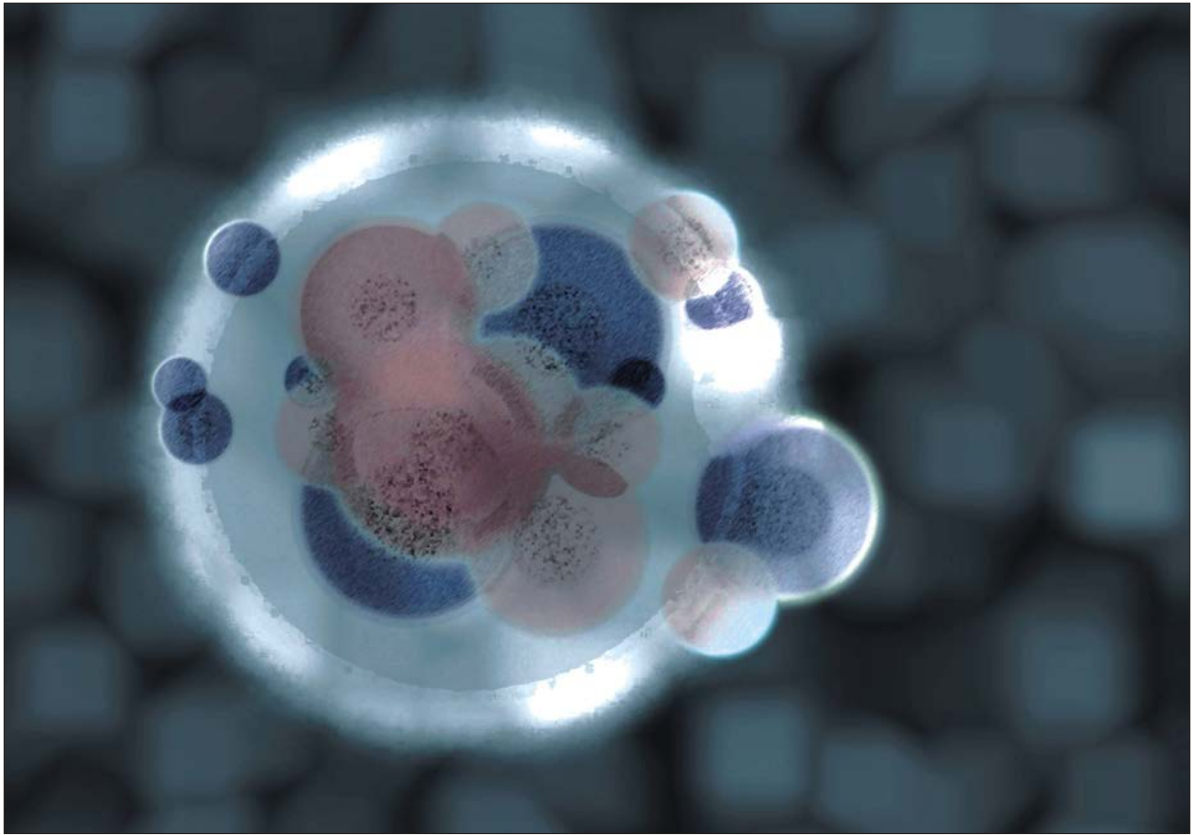




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Genetic Switch for Determining Gender Identified; Gene Linked to So-Called 'Intersex' Families

The Y chromosome is supposed to genetically seal a fetus's fate in terms of gender. Males have one X and one Y chromosome, while females have two X chromosomes. Yet, in some families a child is born with an X and Y chromosome and develops physically as a female, although she may not menstruate, and her brothers and male cousins may have underdeveloped or ambiguous genitalia.

Now, an international team led by Harry Ostrer, MD, Director of the Human Genetics Program at NYU Langone Medical Center, has identified a gene that appears to be an important switch in determining whether the biological program for the development of gender will go according to plan, or if, when mutated, will cause a glitch in the program. They report their findings in the December 2, 2010, issue of the *American Journal of Human Genetics*, published by Cell Press.

"We have discovered a new molecular switch that seems to modulate the pathways between male and female development," says Dr. Ostrer, a Professor of Pediatrics, Pathology And Medicine at NYU Langone Medical Center. The discovery allows researchers to explain the cause of so-called "intersex" conditions. "It is reassuring to patients and their families to know that this happened for a reason," he says. A screening test for the switch has been used in France to identify affected fetuses, children, and adults who are also at increased risk for developing certain types of cancer.

The newly identified gene, called MAP3K1, is not the first to be associated with sex determination. The so-called male gene called SRY was discovered on the Y chromosome 20 years ago, and since then a number of other such genes have been found. "But MAP3K1 may hold the key to understanding how these various genes are connected," says Dr. Ostrer.

Dr. Ostrer and collaborators in England, Australia, and France, spent nine years searching for the gene responsible for disorders of sex determination in two families, one in France and the other in New Zealand, and in several affected individuals. Different mutations in MAP3K1 were found in unrelated individuals. Some of the women in the study with the Y chromosome had only partially developed ovaries, an overdeveloped clitoris, and excessive hair, while others had tumors in their ovaries. Some of the men had a urethral opening on the underside of their penis or had an abnormally small penis. Some were also infertile. All of these individuals had a normal SRY gene, leading the researchers to suspect that MAP3K1 may influence the activity of that gene. Additional experiments in the study provide evidence for how that might be happening.

Approximately, 1 in 1000 individuals is affected by these disorders, says Dr. Ostrer. To better understand the prevalence and identify new genes and pathways, he is setting up a national consortium to sequence the genomes of affected individuals and their parents.

Dr. Ostrer's collaborators include Alexander Pearlman and Johnny Loke at NYU Langone Medical Center, Andy Greenfield at the MRC Mammalian Genetics Unit in England, Andrew Sinclair and Stefan White at the Murdoch Children's Research Institute in Australia, and Cedric Le Caignec and Albert David from the Centre Hospitalier Universitaire de Nantes in France.