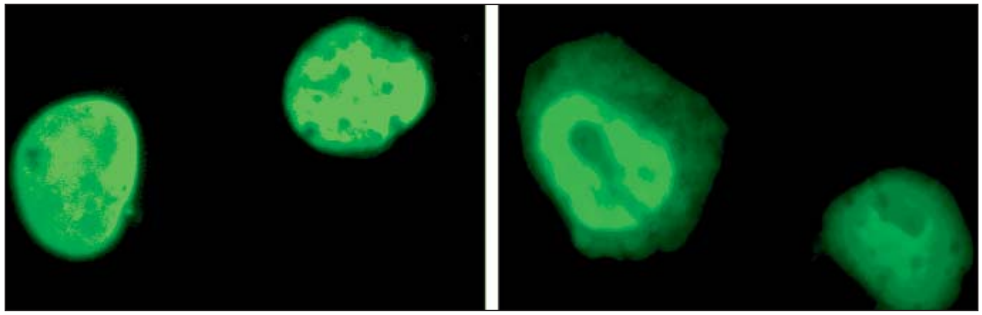
CELL BIOLOGY

# In Sex Reversal, Protein Deterred by Nuclear Barrier

**SAN FRANCISCO, CALIFORNIA**—Each year, a few babies are born with a male set of chromosomes and female sexual organs. This sex reversal, called Swyer syndrome, can happen when changes in a protein called SRY impair its function. Previously reported SRY mutations interfere with the protein's ability to bind to DNA. But recent data, including some presented here this week at the annual meeting of the American Society for Cell Biology (ASCB), show that in some cases, the altered protein has trouble entering the nucleus of fetal male gonadal cells. Thus, genes that should be turned on by SRY to make testes remain off. "We now show a completely different mechanism as to how someone can become an XY female," reports cell biologist David Jans of Monash University in Victoria, Australia.



**Denied entry.** Normal SRY, labeled in green, hastens into cell nuclei (*left*). Some mutated SRY can enter the nucleus (*right*), but much of the protein lingers in the surrounding cytoplasm.

Getting certain proteins in and out of the nucleus is important for normal cellular functions. But Jans, Vincent Harley of Prince Henry's Institute of Medical Research in Victoria, Australia, and colleagues were the first to directly link a defect in nuclear import with a human syndrome. They reported this summer that SRY molecules engineered to have the same changes found in some sex-reversed people seemed to have problems getting into the nucleus of cells. Normal SRY slips into the nucleus readily.

A closer look revealed that a portion of the protein could no longer latch onto importin β, a factor that helps certain molecules slide into the nucleus through pores in the nuclear membrane. Most proteins use a sequence called a nuclear localization signal (NLS) to attract escort molecules such as importin β. SRY has two NLS segments, and if the one that binds importin β is bungled, Jans and Harley reported earlier, not enough SRY gets into the nucleus.

In some sex-reversed people, however, the NLS recognized by importin β is normal, but the other NLS sequence is mutated. What this NLS recognizes was not well known, but it apparently interacts with the calcium-binding protein calmodulin. Jans and colleagues modified the second NLS in SRY molecules as it is mutated in some sex-reversed people. The engineered protein failed to bind calmodulin. And when the researchers repressed calmodulin activity in cells with normal SRY, the protein could no longer easily enter the nucleus, Jans reported at the ASCB meeting.

Whether calmodulin, a protein that has many functions in the cell, facilitates movement into the nucleus has been a controversial subject. The new findings solidify its role in somehow helping SRY inside. This first demonstration that a clinical syndrome can be caused by a molecule's inability to get into the nucleus is likely "just the tip of an iceberg" of diseases with similar mechanisms, says John Hanover, a cell biologist at the National Institute of Diabetes and Digestive and Kidney Diseases in Bethesda, Maryland.

"It's important to understand SRY because it's the master trigger for maleness: With SRY one becomes a male, and without it one becomes a female," says geneticist Eric Vilain of the University of California, Los Angeles. The Jans team hopes to follow defunct SRY molecules in growing mouse fetuses to learn more about how the protein affects the regulation of genes and the formation of male sex organs. "Sex determination is still very poorly understood," Vilain adds. **–APARNA SREENIVASAN**

Aparna Sreenivasan is a writer in Pacific Grove, California.

GENOME SEQUENCING

# Cow Ambles to the Sequencing House

The U.S. Department of Agriculture (USDA), normally loath to back big-budget genetics projects, is offering $11 million to help sequence the cow genome. The funding, announced last week, comes after months of lobbying from bovine enthusiasts and ensures that the project, estimated to cost at least $50 million, will go forward. Four countries—the United States, Canada, New Zealand, and Australia—have contributed a total of $53 million. Proponents claim that the cow genome will help elucidate human diseases and identify gene variants important for agriculture, such as those that promote milk production.

**Rounding up support.** Funding is in place to sequence the cow genome.

Bovine supporters have been eyeing USDA's coffers since last summer, when the last of the other contributions were announced. The National Human Genome Research Institute in Bethesda, Maryland, forked over $25 million; the state of Texas, $10 million; the Canadian government, $5 million; and the governments of Australia and New Zealand, $1 million each. Two-thirds of New Zealand's contribution came from the cattle industry.

Until now, USDA had balked at a big donation: "There's never been enough money in the USDA budget to support large-scale sequencing," says Harris Lewin, director of the Institute for Genomic Biology at the University of Illinois, Urbana-Champaign. In 2003, USDA's extramural research program totaled a mere $166 million out of its $74 billion budget. The agency has helped fund smaller sequences, such as the honeybee's 200 million base pairs. Researchers credit Joseph Jen, the USDA undersecretary for research, education, and economics, with helping convince the agency to contribute to the roughly 3-billion-base-pair bovine sequence.

A Montana Hereford has been anointed the lucky cow. The project will begin at Baylor College of Medicine in Houston, Texas, in the next few months and should be completed within 3 to 4 years. **–JENNIFER COUZIN**

CREDITS: (TOP TO BOTTOM) D. JANS; NHGRI