When More Is Less

FEMALES' POTENTIALLY TOXIC DOUBLE DOSE OF THE X CHROMOSOME APPEARS TO BE OFFSET BY A MOLECULAR "DIMMER SWITCH."

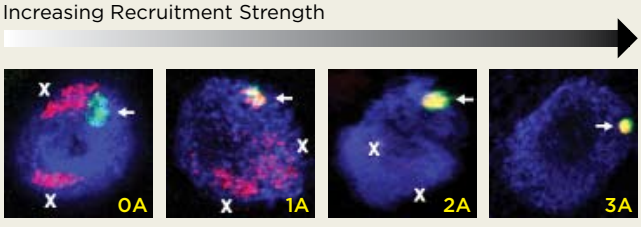
Sugar and spice and X chromosome twice—that's what girls are made of, despite the fact that this double dollop of X chromosomes can be deadly for females of any species. HHMI investigator Barbara J. Meyer and her colleagues at the University of California, Berkeley, study how the roundworm, *Caenorhabditis elegans*, compensates for that second dose.

It turns out that in a *C. elegans* hermaphrodite (a female that makes sperm as well as eggs), gene expression from each X chromosome gets turned down by half—a feat accomplished with a sort of molecular "dimmer switch," Meyer's group has shown. Dubbed the dosage compensation complex (DCC), it covers the length of both X chromosomes but no other chromosomes.

To understand just *how* the DCC represses genes, Meyer's group tackled a more fundamental question: How does the DCC distinguish an X chromosome from other chromosomes in the first place? As they reported in the November 30, 2006, issue of *Nature*, the researchers have made an important discovery that reveals much of the answer. After chopping an X chromosome into small pieces and introducing them into *C. elegans* hermaphrodites one at a time, they identified numerous fragments that could recruit the DCC proteins.

"When we dissected the recruiting fragments further, we narrowed them down to really tiny pieces—only 33 nucleotides in one case," Meyer says. Each site contains patterns of two different nucleotide stretches, termed A and B motifs. Surprisingly, both motifs also occur on the other chromosomes. "But we noticed that each recruitment site contained multiple copies of these motifs. And it's the clustering of these motifs on the X chromosomes that seems to matter," Meyer says.

Meyer speculates that cells may use similar principles to accomplish other chromosome-wide tasks such as DNA replication, chromosome segregation, and other forms of coordinated gene regulation. ■ – PAUL MUHLRAD



DCC recruiting fragments (green, arrows) with multiple A motifs recruit the DCC (red) so strongly in hermaphrodite nuclei (blue), they pull complexes away from X chromosomes. Reducing A motif number by mutation decreases recruitment strength, and DCC binding returns to X.

Patrick McDonald, Jessica Gunther, Judith Jans / Meyer lab

IN BRIEF

San Diego, who led the study reported October 1, 2006, in an advance online publication of *Nature*.

INHERITING A TENDENCY TO BRAIN INFECTION

Might some infectious diseases run in families? Findings from researchers in France support the controversial idea that an error in a single gene is enough to dramatically alter an individual's susceptibility to certain infections. Jean-Laurent Casanova, an HHMI international research scholar at the Necker Medical School in Paris, and colleagues have identified a single gene that predisposes individuals to herpes simplex encephalitis, an infectious disease that tends to be extremely choosy about its victims.

As many as 8 of 10 adults are infected with the herpes simplex virus-1. For most, the worst symptom is a cold sore, but in some individuals the virus causes inflammation of the brain that can lead to mental retardation, epilepsy, or death. Casanova suspected that those susceptible to the disease were genetically predisposed to it and reasoned that the genetic element was probably recessive: an individual had to carry two copies of the affected gene to show the predisposition.

Evidence he collected during an epidemiologic survey in France revealed that a significant proportion of patients with herpes simplex encephalitis had parents who were blood relatives to each other—often first or second cousins—and were therefore at higher than normal risk of inheriting two copies of a faulty gene. In a report in the October 13, 2006, issue of *Science*, the team described two young patients with mutations in this gene who are susceptible to the disease; otherwise, they are immunologically normal.

FOCUSING IN ON CANCER'S COMPLEXITY

In the first large-scale screen of genetic changes in cancer cells, researchers have found that a typical breast or colorectal tumor results from mutations in about 90 genes, with different sets of mutations producing the same type of cancer. But the many different genetic routes to malignancy share features that point toward new means of cancer prevention, diagnosis, and treatment. Previous genetic studies of cancer have concentrated on specific genes or chromosomal regions.

In the October 13, 2006, issue of *Science*, HHMI investigators Bert Vogelstein at the Johns Hopkins University and Sanford D. Markowitz at Case Western Reserve University School of Medicine, together with colleagues, report a radically new way of identifying genes involved in cancer. They screened 13,000 of the well-annotated human genes that all major genomic centers agree encode proteins. They first looked for mutations in 22 cancerous breast or colorectal tumors. From that list, 191 genes appeared to be particularly important. Extrapolating to the total number of genes in the human genome, the researchers determined that about 17 genes are likely to be critically involved in the development of each type of cancer.

"Scientists who have seen these data have told us that it keeps them up all night thinking," says Vogelstein. "It will hopefully open up a large number of opportunities in many areas of cancer research."