Keeping chromosomes from cuddling up

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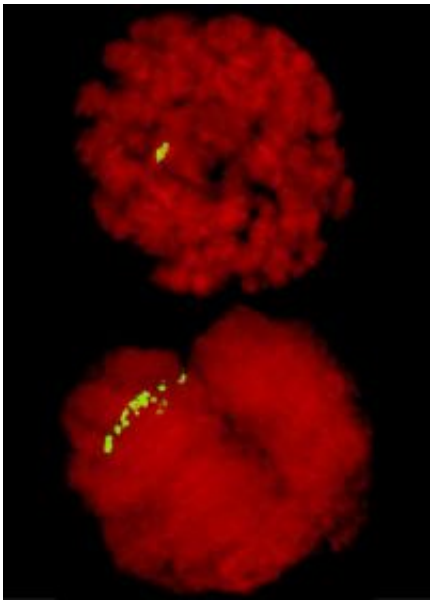

The red balls are each false-color digital images of a nucleus of a fruit fly salivary gland cell. The nuclei are 50 micrometers in diameter, about one-half the width of a human hair. Each ball is composed of about 2,000 chromosome fibers. The yellow-green dots, multiple copies of a specific gene marked by green fluorescent protein (GFP), are all snuggled up together in the top image, the nucleus without condensin II. The bottom image shows how the GFP-marked genes are moved apart after condensin II is produced in the nucleus. Credit: Helen F. Smith, The University of Arizona

If chromosomes snuggle up too closely at the wrong times, the results can be genetic disaster. Now researchers have found the molecular machines in fruit flies that yank chromosomes, the DNA-carrying structures, apart when necessary.

The machines, proteins called condensin II, separate chromosomes by twisting them into supercoils that kink up and therefore can no longer touch.

Scientists had known of condensin II but did not know how it functioned inside cells.

Keeping specific parts of chromosomes from touching can change how the instructions carried in the DNA are read, said research team leader Giovanni Bosco of The University of Arizona in Tucson.

"It's like picking up your favorite book and, depending on what chair you chose to sit in, it turned into a different story -- even though the printed words in the book never changed," Bosco, a UA assistant professor of molecular and cellular biology, wrote in an e-mail.

"This now changes the way we think about genetic information. Taking a literal reading of it is not what actually happens," he wrote. "Instead, context matters."

The team also found that condensin II plays a key role in making sure that fruit fly sperm cells each receive the proper number of chromosomes -- not too many, not too few.

Bosco suspects that condensin II plays the same role in the formation of human sperm and eggs.

Having too many or too few chromosomes in egg or sperm cells is the source of several important genetic disorders, including Down syndrome.

Abnormalities in chromosome number is also the cause of some miscarriages of early-term fetuses in humans.

The research will be published in two separate papers. "Chromosome Alignment and Transvection are Antagonized by Condensin II," by Tom A. Hartl and Helen F. Smith, UA doctoral students, and Bosco is scheduled for publication in the Nov. 28 issue of the journal *Science*. Bosco is also a member of UA's BIO5 Institute.

Hartl, Sarah J. Sweeney and Peter J. Knepler, both at the UA, and Bosco published their paper, "Condensin II Resolves Chromosomal Associations to Enable Anaphase I Segregation in Drosophila Male Meiosis," in the October 2008 issue of *PLoS Genetics*. Sweeney and Knepler were UA undergraduates when they conducted the research.

The National Institutes of Health and the National Science Foundation funded the research.

Learning how cells control chromosomes and how DNA is transcribed will lead to better understanding of how an organism's DNA affects the organism's final form.

Scientists have known for about 50 years that when chromosomes are in direct contact, the transcription machinery can choose to transcribe either the gene from the mother or the gene from the father.

Many researchers investigated how the specific genes were brought close together so that process, known as transvection, could happen.

Bosco wondered, what if the chromosomes stayed stuck together?

To find something that separated chromosomes, he looked for female fruit flies that were sterile because chromosomes in their eggs had stuck together.

Once he had those fruit flies, Hartl isolated the gene that kept the

chromosomes from coming apart. He found that the gene coded for condensin II, indicating that the sterile flies couldn't make condensin II.

To be able to watch how condensin II affects chromosomes, the researchers used the salivary glands from normal Drosophila melanogaster fruit flies. Fruit fly salivary glands are unusual, because they have many copies of the same chromosome coiled together like a rope.

Hartl said, "You can actually see chromosomes, because the cells are so huge and the chromosomes are so huge."

The team inserted an additional gene into the chromosomes that would turn the condensin II-producing gene off at 77 F (21 C) and on at 95 F (35 C). The researchers also marked one gene on the chromosomes with green fluorescent protein, or GFP, to be able to see changes in the chromosomes' positions.

The scientists then looked at the salivary glands at the two temperatures to see what happened when condensin II was present and when it was absent.

Bosco said, "Simply turning the condensin gene on or off, we could watch the chromosomes move right before our eyes, demonstrating that condensin was mostly likely the tiny machine that was ripping the chromosomes apart."

He said these findings are significant because more and more genetic tests to sequence people's DNA are becoming available, but the DNA sequence alone does not completely determine what diseases the person will have.

Even if it's in the genes, it might not show, he said. "It's what your cells

are doing with your genes that's important."

To pull the chromosomes apart, condensin II changes its shape. Smith said the team's next step is figuring out how condensin II proteins are recruited to the chromosomes and how the condensin II proteins use the cellular energy packets known as ATP to change shape.

Source: University of Arizona