

## NIEHS study on genome stability highlighted in Genetics

By Staton Wade

The negative impacts of genome instability are clear, but how can genome instability confer an adaptive advantage to cells under environmental stress? A new study from NIEHS investigators addressing this question is published in the February issue of the journal *Genetics*. The findings suggest mechanisms that may be employed by cancer cells or pathogenic fungi on the path to drug resistance.

The [study](#),

(<http://www.ncbi.nlm.nih.gov/pubmed/24298060>)

first published online in December 2013, found that defects in the sister chromatid cohesion (SCC) pathway led to chromosome instability, which allowed yeast to survive toxic environmental exposures. Shay Covo, Ph.D., is the corresponding author on the paper and a former postdoc in the NIEHS Laboratory of Molecular Genetics. He performed the work while in the [Chromosome Stability Group](#) led by Michael Resnick, Ph.D.

### Addressing cancer using a simple model organism

Covo and his colleagues designed a novel assay to study the rate of aneuploidy, or the gain or loss of entire chromosomes, in different yeast strains in response to copper exposure. While previous work has addressed chromosome loss, this assay allowed the researchers to focus on chromosome gain and to identify the nature of the aneuploidy that arose. "We were the first to combine a quantitative measurement of the rate of chromosome gain within a population with a detailed analysis of the karyotype [a visual representation] of some of the isolates within the population," explained Covo.

Using the assay, the researchers found that single mutations in the SCC pathway could greatly affect genome instability, as determined in the lab of their collaborator, [Lucas Argueso, Ph.D.](#),

([http://www.cvmb.colostate.edu/erhs/faculty/argueso/\\_argueso.html](http://www.cvmb.colostate.edu/erhs/faculty/argueso/_argueso.html))

at Colorado State University. They observed copper resistant mutants with surprisingly imbalanced genomes.

"We had an isolate in which the degree of aneuploidy was 33 percent of the entire genome," Covo said. "Such events are seen in cancer, but to observe them in a simple model system, after a short selection period, is impressive."

The study's model provides a great opportunity to explore carcinogenic mutations and genome instability in a tractable system. Defects in SCC are known to play a role in tumorigenesis. "These results may explain why similar types of mutations are so frequent in tumors and how the imbalanced genomes often seen in cancer can actually arise," said Covo. "One can now ask what genetic and environmental determinants play a role in such phenomenon."

The work also suggests a mechanism by which single-celled organisms can easily adapt to a stressful environment. As Covo pointed out, "Since the work was done in yeast, our results are even more relevant to diseases caused by other yeast such as *Candida albicans*. It is known that drug resistance among *Candida* species is associated with chromosome gain."

Since the completion of the yeast study, Covo has started [his own lab](#)

(<http://departments.agri.huji.ac.il/plantpath/covo/>)

in the Department of Plant Pathology and Microbiology at the Hebrew University of Jerusalem (see [story](#)). He is currently applying the rationale developed for his work at NIEHS to a more general agricultural system to study pesticide and fungicide resistance. Covo said that having his work highlighted by *Genetics* has increased interest and requests for reprints, which he hopes will lead to more chances for collaboration.

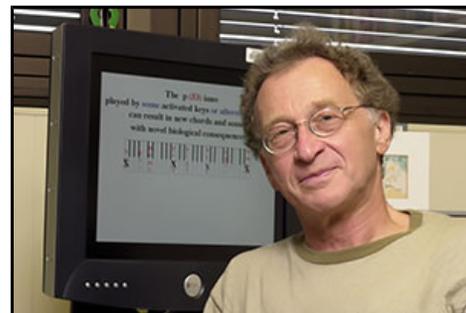
Citation: [Covo S, Puccia CM, Argueso JL, Gordenin DA, Resnick MA.](#)

(<http://www.ncbi.nlm.nih.gov/pubmed/24298060>)

2014. The sister chromatid cohesion pathway suppresses multiple chromosome gain and chromosome amplification. *Genetics* 196(2):373-384.



*Covo and colleagues used a novel assay to study chromosome gain in yeast and measure properties that cannot be properly addressed with chromosome loss assays. (Photo courtesy of Steve McCaw)*



*Resnick's leadership encouraged the kind of open-ended inquiry that helped Covo flourish as a researcher during his training at NIEHS. (Photo courtesy of Steve McCaw)*

(Staton Wade, Ph.D., is an Intramural Research Training Award fellow in the NIEHS Chromatin and Gene Expression Group.)

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