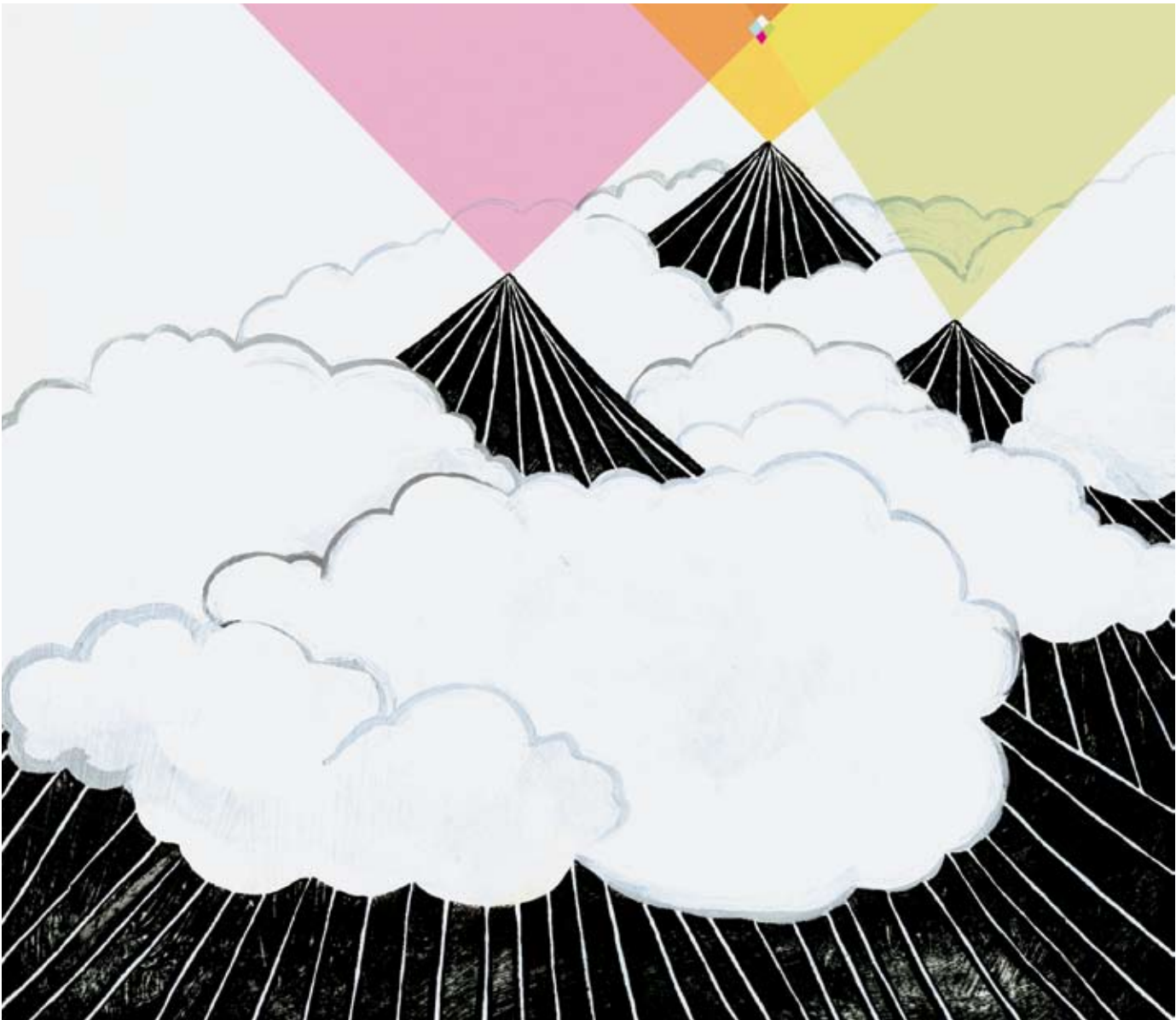


# A No-Nonsense Approach to Gene Relationships

*Researchers use their large gene database to find an elusive enzyme.*



LIKE A CASSETTE IN A TAPE DECK, DNA IS ESPECIALLY VULNERABLE TO damage while it is being copied. A particular protein modification is known to protect cell integrity during replication, but despite efforts by several well-established laboratories, the trigger for this event has been a mystery. ¶ Using a technique they developed to assemble

large-scale gene-interaction databases, HHMI investigator Jonathan S. Weissman, HHMI postdoctoral fellow Sean Collins, and colleague Nevan Krogan—all at the University of California, San Francisco (UCSF)—discovered more quickly than other labs that the mystery protein is an

enzyme called Rtt109 (see sidebar, “The Protective Trigger”).

Score one for E-MAP, a technique the scientists unveiled in 2005 to enhance studies of gene-gene, or epistatic, interactions. E-MAP stands for epistatic miniarray profiles. “It provides functional information that you just can’t get any other way,” notes Harvard Medical School biochemist Kevin Struhl. “It provides more detailed and comprehensive information than smaller studies can.”

Weissman explains its purpose: “E-MAP is an automated technique to rapidly and systematically catalog how individual genes work together in a cell.” Traditionally, biologists study gene interactions in yeast by eliminating or damaging an individual gene in a laboratory cell sample, pairing the resulting mutant with others, and observing whether the cells live or die. The drawback of this method is that it is slow and painstaking, and it requires subjective choices: which genes to select for study, which mutants to pair with which others.



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JONATHAN WEISSMAN

For example, the budding yeast, *Saccharomyces cerevisiae*, contains about 6,000 genes. To analyze every gene-gene interaction would mean testing a daunting 18 million gene pairs. Scientists have devoted years to scrutinizing a few gene relationships of interest, knowing that, as a practical matter, they are ignoring others. Not necessary with E-MAP.

Krogan compares E-MAP to finding the light switch after stumbling around with just a flashlight. “With a flashlight, you see things in bits and pieces. With the lights on, you see how everything is connected.”

To develop their most recent E-MAP, the UCSF group selected 743 genes in *S. cerevisiae* that code for a group of proteins involved in maintaining, replicating, and translating DNA to RNA. The team created double mutants from every possible combination of the genes—more

than 200,000 gene pairs. Using software they developed, they compared the double mutants’ growth rates with growth rates for single mutants. The result, detailed in an advance online publication in the journal *Nature* on February 21, 2007, was an atlas of how every gene they tested communicates with the others.

The scientists wanted to eliminate any preconceived biases in selecting the gene pairs to study, and they wanted a more nuanced picture of how particular combinations of genes affect cell function. “It’s one thing to say that a double mutant is dead—dead is very clear,” Weissman says. Harder to analyze but equally important are the subtler cases, where double mutations sicken a yeast colony, but less so than a single mutation would, or where they actually make a colony healthier.

Because the database currently covers only a small percentage of all yeast genes, says Harvard’s Struhl, its usefulness is limited to researchers who happen to be interested in those genes. “A whole-genome analysis would be a great boon,” he says.

Weissman and colleagues are working on expanding the method to the rest of the yeast genome—and then to other organisms, including humans. Meanwhile, the scientists have made the atlas freely available on the Web (<http://interactome-cmp.ucsf.edu>) so that other researchers can mine the database for gene-gene interactions. ■ —SIRI CARPENTER

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## THE PROTECTIVE TRIGGER

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**RESEARCHERS HAD NOT SUSPECTED** Rtt109’s protective role because it bears no structural or chemical resemblance to the group of proteins believed to do that work, explains Jonathan Weissman. It turns out that the enzyme marks chromosomal components called histones to signal that a particular stretch of DNA has already been copied. This chemical cross-checking is essential to preventing DNA damage during replication. >> **ABOUT THE SAME** time Weissman and colleagues published their results in early 2007, three other groups, using more conventional approaches, also reported Rtt109’s role in protecting DNA. But to do so, Nevan Krogan observes, took laborious screening through the entire yeast genome. In contrast, the E-MAP database allowed the UCSF group to narrow the possibilities to just a handful of promising proteins. “We came to the same answer,” says Krogan, “but in their case, it took years of work. In ours, it took months.” — S.C.