

RIGHT — “THE INTERACTIONS WE’RE DISCOVERING AMONG YEAST GENES THAT ARE CONSERVED IN HUMANS,” CHARLES BOONE SAYS, “MAY VERY WELL BE IMPORTANT FOR HUMAN DISEASE.”

Uncovering Genetic Combinations

Researchers systematically identify critical gene interactions in yeast.

MOST TRAITS THAT ARE INHERITED, INCLUDING THOSE THAT predispose individuals to certain diseases, are conferred not by single genes but by combinations of them.

That’s both good news and bad news, says Charles Boone, an HHMI international research scholar at the University of Toronto. The good news is that genomes have a remarkable capacity to buffer themselves against potential harm from mutations. “Biological systems have evolved to be robust,” he explains. “They can withstand all sorts of environmental and genetic perturbations.” Most higher organisms have multiple sets of genes performing similar duties, “like backup systems.”

The bad news is that all this genetic redundancy presents a challenge to disease detectives. The more genes that contribute to a particular condition, the more avenues researchers must follow to find the responsible genes and possible treatments.

To help meet that challenge, Boone and colleagues turned to baker’s yeast, a single-celled fungus containing some 6,000 genes, roughly a quarter of the estimated number in humans. “A large fraction of yeast genes are ‘conserved,’ meaning that they have structurally and functionally related counterparts in higher organisms,” says Boone.

Boone’s team devised a method, called synthetic genetic array, or SGA, analysis, to systematically identify gene interactions in yeast. (The study was published in *Science* in 2001.) The approach works by uncovering genetic redundancy.

Boone notes that almost 5,000 of the yeast genes are “nonessential,” the functions of most of them being covered by backup genes. If any of those genes are damaged or wiped out by a mutation, the yeast cell normally can function fine. But geneticists have observed that if they combine pairs of mutations, some rare combinations—those involving genes that normally cover for each other—cause the cells to die. They call that phenomenon “synthetic lethality.”

Boone and his former graduate student, Amy Hin Yan Tong, teamed with an international group of collaborators in an



PETER STIBALD

effort to map every such genetic interaction in yeast. Their approach was to generate double mutants that represent each pairwise combination of all the nonessential genes and then catalog which pairs are lethal.

To combine two mutations in yeast, geneticists first have to cross two strains, each having a single mutation. Boone’s team rigged robots to handle all the crosses, thousands at a time.

“There’s a huge number of synthetic-lethal interactions,” Boone reports after analyzing only 4 percent of all the possible gene combinations. (The analysis was published last year in *Science*.) Interactions occur predominantly between genes involved in the same general process, such as DNA replication, chromosome segregation, or secretion. However, Boone says, “some incredibly interesting interactions are those that illuminate connections between different processes, such as interactions that link chromosome architecture to cell morphology.”

“Looking at the double mutants really sorts things out, identifying pathways and complexes that cooperate to drive essential cellular functions” Boone says. “So now, instead of just gathering collections of genes, we’re actually drawing the scaffold, or wiring plan, of the organism.”

Yeast geneticist and Nobel laureate Lee Hartwell says of Boone’s research, “Many approaches to interactions measure physical interactions that may or may not be functionally important. The significance of this work is that it is identifying functionally important interactions and has the capacity to do so in a genome-wide manner.”

Of course, one of the goals of yeast research is a better understanding of human biology. “We hope to map these networks in yeast, and then, using different technologies, to map relevant parts of them in higher organisms like worms, flies, and mice,” Boone explains. And because of the strong kinship between these organisms’ genomes, Boone says that mapping their gene networks may paint a picture of similar networks at work in humans. ■

—Paul Muhlrads