



UNH Hubbard Center: New Research On Mutation In Yeast Can Enhance Understanding Of Human Diseases

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DURHAM, N.H. - Yeast, a model organism heavily relied upon for studying basic biological processes as they relate to human health, mutates in a distinctly different pattern than other model organisms, a finding that brings researchers closer to understanding the role of evolutionary genetics in human diseases and cancer. The study, by researchers from the University of New Hampshire, Indiana University, Harvard University, and the University of Utah, appears in Proceedings of the National Academy of Science (PNAS) Online Early Edition this week (June 16 - 20, 2008).

"In biology, the mutation is an absolutely fundamental process, essential to evolution but also the source of all genetic disease," says Kelley Thomas, associate professor of biochemistry and director of the Hubbard Center for Genome Studies at the University of New Hampshire. "Despite its importance, we still don't know much about the basic processes of mutation." Cancers are caused by mutations, as are inherited diseases like Huntington's disease and fragile X syndrome, the most common inherited form of mental retardation.

"If we know more about the patterns of mutation, we'd be able to better understand the origins of these diseases - and maybe prevent them," says Thomas.

The researchers asked a fundamental question: "What is the baseline rate and spectrum of mutation in yeast?" They found that, like the previously studied mutations in the nematode *Caenorhabditis elegans*, the yeast *Saccharomyces cerevisiae* had a very high rate of mutation from generation to generation.

Its patterns of mutation, however, turned out to be unique. While *C. elegans* mutations were largely the result of inserting or deleting base pairs of DNA, yeast's patterns of mutation were characterized by changing one base pair for another. "That was really surprising, that we didn't find that adding or subtracting in yeast," says Thomas. He adds that the consequences of inserting and deleting base pairs can be much more dramatic than substituting one base pair for another.

Comparing the mutation rates and spectrums of these two model organisms informs researchers' assumptions about mutation relevant to human health. "We were surprised that there isn't a common spectrum of mutation," says Thomas. "However, it's exciting, because if we can describe patterns of mutation, maybe we can understand why some organisms, including people, are susceptible to certain mutations and not others."

The approach used in this study allows yeast to accumulate mutations in the near absence of natural selection. By doing this, cells with mutations that might otherwise be lost because their cell is outgrown by others can continue to survive and be analyzed for their mutations. With this study, Thomas and his colleagues overcome a major limitation to the study of mutation by using a new generation of sequencing technology that let them sequence the entire genome of each yeast strain and to identify the rare mutational events that have taken place. This way, the yeast accumulate mutations that might otherwise make them "bad yeast" - the weak survive - and look for them across the entire 10 million base pair genome.

"The beer you make with this yeast is horrible," Thomas jokes.

Indiana University's Michael Lynch was the principal investigator on this paper, "A Genome-wide view of the spectrum of spontaneous mutations in yeast." Thomas credits former UNH graduate student Shilpa Kulkarni and current graduate student Way Sung with contributing powerful bioinformatics work to this research, which he calls "a big computational problem" due to the volume of data. Other UNH contributors from the Hubbard Center were Krystalynne Morris and Kazufusa Okamoto. Daniel Hartl, Christian Landry and Erik Dopman from Harvard; Nicole Coffey from Indiana University; and W. Joseph Dickinson from the University of Utah also contributed. The work was supported by the National Institutes for Health.

The Hubbard Center for Genome Studies at the University of New Hampshire was established in 2001 to lead the development of genomics research at UNH. It is a leader in comparative and environmental genomics, with a special emphasis on novel model species.

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