UNIVERSITY OF NEBRASKA–LINCOLN

NEBRASKA TODAY

January 13, 2017

Study refutes how fruit flies developed alcohol tolerance

by Leslie Reed | University Communication (/written-by/leslie-reed-university-communication/)

Craig Chandler | University Communication

Kristi Montooth, an associate professor in the School of Biological Sciences, displays a bottle containing fruit flies that are the subject of her research. She is a co-author of a new scientific paper investigating the evolutionary causes of fruit flies' tolerance for alcohol.

The common fruit fly, the tiny insect drawn to your beer or wine, has evolved to have an impressive tolerance for alcohol.

More than two decades ago, in one of the first papers using gene sequences to find signatures of natural selection, scientists hypothesized that a molecular change in an enzyme gave the *Drosophila melanogaster* fruit fly species its superior ability to metabolize alcohol. Scientists concluded that the change they found in the Alcohol dehydrogenase (ADH) protein could be the adaptation that allowed *D. melanogaster* to colonize ethanol-rich habitats in rotting fruit better than its nearly identical relative, *Drosophila simulans*.

It seemed a logical conclusion that the gene sequence changes that altered amino acids in an enzyme that breaks down alcohol would be the mechanism of natural selection.

However, the authors of a new paper published online Jan. 13 by Nature Ecology & Evolution say they have now refuted that hypothesis.

Their findings indicate that intuition and signatures of selection in gene sequence may not be enough for scientists to conclusively solve the puzzles of molecular evolution. Tests also are needed to check how the changes function in organisms.

Using genetic engineering, scientists resurrected the fruit flies' ADH protein from ancestral species to compare whether the amino acid changes that have occurred in *D. melanogaster*'s ADH enzyme actually improved the fruit flies' ability to tolerate alcohol. The answer, conclusively, was "no."

"This paper takes advantage of modern molecular biology and genetic approaches to test some of those hypotheses," said University of Nebraska-Lincoln biologist Kristi L. Montooth, a fruit fly expert who co-authored the new study. "It doesn't dispute that this species has a high ethanol tolerance. But it suggests that the molecular changes that have led to that high tolerance are not in this protein. They must be in other genes in the genome."

The search for new pathways in fruit flies could offer new clues about alcohol tolerance in humans, Montooth added.

Montooth and University of Chicago researcher Mohammad A. Siddiq conducted experiments with living transgenetic flies in her Lincoln laboratory during October 2015. They found the ADH amino acid changes made no discernible difference in the species' ability to survive while being fed increasingly heavy doses of alcohol. The flies had been genetically engineered by University of Wisconsin researcher David Loehlin so that their only genetic difference was in the ADH protein sequence.

The experiments with living fruit flies supported the findings of other experiments investigating the enzyme's biochemistry.

With molecular evolution, scientists seek to identify the specific molecular changes underlying the trait changes that shape the evolutionary family tree.

"We're generating so much sequence data right now, from so many species, that it's relatively straightforward to look for signatures of selection in genes and to find good candidates for adaptations," Montooth said. "But those are just candidates. You have to functionally test them if you want to say those are the variants favored by natural selection."

Siddiq and Montooth began working together in 2008 after Siddiq took the freshman biology course Montooth taught while on faculty at Indiana University. He began working in her laboratory and co-authored research with her while he was an undergraduate student.

"Despite now being in my fifth year of graduate school, I'm still publishing papers with the professor that I met on my first day of college," Siddiq said.

Siddiq, who is the study's first author, is now pursuing a doctoral degree at the University of Chicago, where he is studying with co-author Joseph W. Thornton, a professor who studies the molecular mechanisms of evolution. David W. Loehlin, a post-doctoral researcher at the University of Wisconsin-Madison, also participated in the study, creating the transgenic flies used in the experiments.

Siddiq came to Lincoln to work with Montooth on the fruit fly study, he said, because of her experience and expertise in evolutionary physiology and because of her influence on his career.

"I took her introductory biology class (as a college freshman) and loved it because her passion for evolution and its role as a unifying principle in biology really came through," Siddiq said. "My appreciation for studying traits not only in the test tube, but in the level of organisms, comes from the experiments I did during my undergraduate years. "

The new study is the first demonstration of an approach combining ancestral sequence reconstruction with the making of transgenic organisms to directly test hypotheses at multiple biological levels, Siddiq said. It's a broadly applicable approach that in theory could be used with other organisms that lend themselves to transgenic engineering.

"One of the neat things about this paper is that it looks at the effects of this gene's mutations at the level of how the enzyme functions in the test tube, how it functions in the fly and then the consequences for how the fly deals with ethanol," Montooth said. "It's looking at effects of mutations across different levels of biological organization. Each of the co-authors played a role by investigating a different level of organization."

The study received funding through the National Science Foundation and the National Institutes of Health, including an NIH training grant and NSF fellowship for Siddiq and an NSF CAREER award for Montooth. Loehlin received support from a Howard Hughes Medical Institute postdoctoral fellowship.

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Kristi Montooth, Associate Professor, Biological Sciences (mailto:kmontooth2@unl.edu)
402-472-8455 (tel:402-472-8455)
Website (http://biosci.unl.edu/kristi-montooth)

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(https://news.unl.edu/sites/default/files/media/2017C montooth-02.jpg)
Montooth co-authored a paper investigating evolutionary changes in fruit flies with Mohammad Siddiq and others. Siddiq, now pursuing a doctorate at the University of Chicago, began conducting research with Montooth when he was an undergraduate student at Indiana University. This photo was taken in 2012 while Montooth was on the Indiana faculty.

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