# Form or function? Evolution takes different paths

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Biologists long have known that both the appearance of organisms and their inner workings are shaped by evolution. But do the same genetic mechanisms underlie changes in form and function? A new study by scientists at the University of Michigan and Taiwan's National Health Research Institutes suggests not.

The research is scheduled for online publication in the Proceedings of the National Academy of Sciences during the week of April 5.

In the study, U-M evolutionary biologist Jianzhi "George" Zhang and colleagues Ben-Yang Liao and Meng-Pin Weng set out to systematically test a hypothesis proposed by molecular biologist Sean Carroll in 2005. Carroll posited that changes in morphology (such things as shape, color and structure of external and internal parts) occur through different genetic mechanisms than changes in physiology (inner workings). Carroll backed up his assertion with examples, but the idea, which challenged previous dogma, was controversial, Zhang said.

To test the hypothesis, Zhang's team turned to a database of knockout mice---lab mice that have been engineered to lack particular genes.

"We found about 5,200 genes that have been knocked out in the mouse and the resulting effects studied," said Zhang, a professor of ecology and evolutionary biology. "From those genes, we looked for genes that, when knocked out, affect only morphological traits, not physiological traits. We got about 900 of those genes, which we call morphogenes."

The researchers also found about 900 "physiogenes"---genes that affect only physiological traits, not morphology.

"Next, we compared the two groups of genes to see if there are differences in the molecular roles of their products," Zhang said. "We found very large differences." Morphogenes were more likely to carry instructions for transcription---the step that determines whether a gene should be turned on and how much gene product should be manufactured. Physiogenes were more likely to be blueprints for enzymes, receptors, transporters and ion channels (molecules that control the flow of ions across cell membranes).

The next step was to examine patterns of evolution in the two groups of genes.

In a classic paper published in 1975, evolutionary biologists Mary-Claire King and Allan Wilson argued that evolution of both morphology and "ways of life" (physiology and behavior) occurred through changes in the way genes are turned on and off, rather than through direct changes in gene products themselves. In the parlance of geneticists, these traits were shaped over time through changes in gene expression, not changes in protein sequence. King and Wilson supported their claim with the example of chimpanzees and humans, which are remarkably similar at the protein sequence level, but quite different in appearance and behavior. It was this influential paper that Carroll commemorated 30 years later, but he suggested instead that physiological changes are due to protein sequence changes, while morphological changes result from changes in gene expression.

With their new analysis, Zhang and colleagues found that, at the protein sequence level, physiogenes evolved much faster than morphogenes. "This is consistent with the idea that physiological changes tend to be caused by protein sequence changes," Zhang said.

Next, the researchers examined gene expression data, looking to see how similarly or differently genes are turned on or off in identical tissues from different species, such as the livers of mice and humans. Greater differences indicate more rapid evolutionary change.

"We found more differences in morphogenes than in physiogenes," Zhang said. "In other words, morphogenes evolve faster, with respect to expression patterns, than do physiogenes---a finding that supports the idea that morphological changes result mainly from gene expression changes."

The finding that morphology and physiology are shaped by different evolutionary genetic processes can not only aid in future evolutionary studies, but can also be helpful in the study of human disease, Zhang said. "Our analysis of the knockout mouse data suggests that morphological defects are more likely due to problems with gene expression. This knowledge could help identify the disease-causing mutations more quickly, because it narrows the set of candidate genes and mutations that one needs to search from."

**More information:** Proceedings of the National Academy of Sciences: www.pnas.org/

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