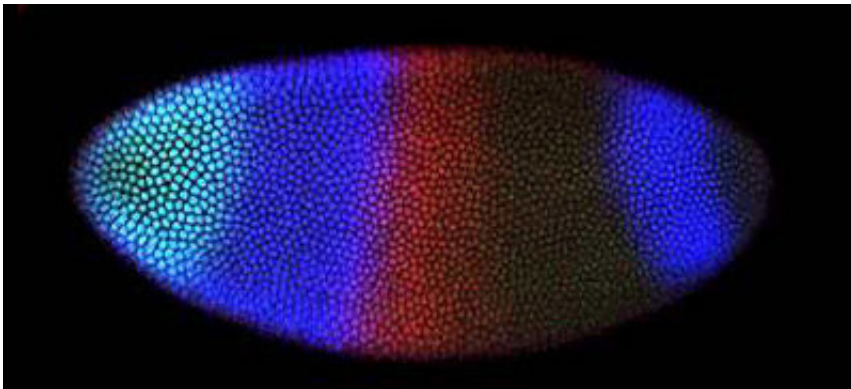


Scientists go 'back to the future,' create flies with ancient genes to study evolution

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Early fly embryo stained for three Bcd target genes, Otd (light blue), Hb (dark blue), and Kr (red). Credit: Rhea Datta.

Scientists at New York University and the University of Chicago have created fruit flies carrying reconstructed ancient genes to reveal how ancient mutations drove major evolutionary changes in embryonic development—the impact of which we see today.

The work, published in the journal *eLife*, found that two [mutations](#) that arose 140 million years ago changed the function of a critical developmental gene, which now regulates [development](#) of the head and other structures in virtually all species of present-day flies.

"By introducing individual mutations that happened in the deep past into the ancient [genes](#), we were able to show precisely how each one affected

development many millions of years ago," explains Stephen Small, an NYU biologist and one of the paper's senior authors.

"We found that just two chance mutations were the major causes of a profound change in the animal's developmental processes—a change that became indispensable in all of its present-day descendants," says Joseph Thornton, the paper's other senior author and professor of Ecology and Evolution and Human Genetics at the University of Chicago.

Scientists have long sought to understand how genetic mutations changed embryonic development to yield the diverse animal forms we see today. But identifying the important mutations is very difficult because they occurred in the deep past, in long-extinct animals, and they have usually been mixed up with scores of subsequent mutations.

The laboratories of NYU's Small and the University of Chicago's Thornton approached this problem in an innovative way: computationally inferring ancient gene sequences based on their modern descendants, chemically recreating the genes, and then putting them into fly embryos, thereby creating transgenic embryos—i.e., those inserted with a foreign gene—to follow their effects on development in the laboratory.

The study is the first to use ancestral reconstruction in the field of the evolution of development, or evo-devo.

The researchers focused on the evolution of a gene called bicoid. Bicoid triggers the formation of structures at the head (anterior) end of embryos in the fruit fly, an important model organism because many aspects of its genetics and development are shared with humans and other animals. Bicoid serves as the "master regulator" of anterior development by turning on expression of a set genes that carry out head development and suppress tail development, and doing so only at the anterior end.

Bicoid has long presented an evolutionary puzzle. Fly embryos lacking active Bcd protein die very early because instead of forming a head they form tail structures at both ends. But the bicoid gene does not even exist in other insects or more distantly related animals, which use other genes to control anterior development. Bicoid shows that even the most fundamental aspects of development can change drastically during evolution, but how that process occurs is unknown.

The Small and Thornton laboratories sought to understand how bicoid evolved its new developmental function through several means: recreating the precursor gene from which it evolved, characterizing its biochemical functions, introducing it into modern-day fruit flies whose own bicoid gene had been removed, studying its effects on the formation of head structures and expression of the specific genes that drive head development, and introducing historical mutations into the ancestral gene to determine their effects.

Their initial results showed that flies carrying the precursor gene fail to develop a head, with tails at both ends and none of the key genes involved in head development properly expressed. The group then introduced into the precursor gene every mutation that happened during the ancient interval during which bicoid evolved its new role.

Most of the changes had little or no effect on bicoid's functions, but two of them together allowed bicoid to activate a completely new set of target genes. When introduced into fly embryos, this evolutionary mutant version of bicoid activated most of the genes involved in head development in their proper places, and the embryos formed recognizable, albeit incomplete, head structures instead of tail structures at the anterior end.

The group concluded that these two mutations, when combined, were the predominant causes of bicoid's functional evolution, with additional

mutations during the same ancient period fine-tuning the gene's new function.

"By combining the most advanced techniques from developmental biology and evolutionary genetics, we were able to dissect how molecular changes in an ancient gene fundamentally changed one of the most important—and otherwise conserved—processes in animal development," Small notes.

More information: Qinwen Liu et al, Ancient mechanisms for the evolution of the bicoid homeodomain's function in fly development, *eLife* (2018). [DOI: 10.7554/eLife.34594](https://doi.org/10.7554/eLife.34594)

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