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Flies with inner ears?

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In a study which suggests that genetic mutation was not necessarily the primary evolutionary force producing morphological change in mammals, researchers report in the September issue of *Developmental Cell* that the *Drosophila Hmx* gene partially rescued the development of the mouse inner ear, revealing that the gene could direct the development of an organ it does not even possess.

When thinking of how new traits evolve, people have mainly focused upon mutations in protein sequences said Thomas Lufkin, of the Genome Institute of Singapore, and senior author of the *Developmental Cell* study. "But, an equal possibility is that, instead of the gene sequence mutating, the same gene can acquire new expression domains," Lufkin told us.

This possibility became apparent as Lufkin, lead author Weidong Wang, and their colleagues began to study a family of homeobox genes termed Hmx. *Drosophila* has a single *Hmx* gene, termed *DHmx*, whose expression pattern suggests it is involved in the development of the *Drosophila* central nervous system (CNS). Two mouse *Hmx* genes, *Hmx2* and *Hmx3*, are also involved in CNS development, but have additional roles in sensory organ development. Thus, Lufkin and colleagues wondered what *Hmx* functions were conserved during evolution.

The researchers began by analyzing the phenotypes of *Hmx2-/-*, *Hmx3-/-* and *Hmx2-/-/Hmx3-/-* knockout mice, revealing *Hmx2* and *Hmx3* to have overlapping and distinct functions during development of the mouse inner ear. They went on to create a mouse line with the *Drosophila DHmx* gene replacing *Hmx3* and *lacZ* replacing *Hmx2*. As might be expected, *DHmx* rescued murine CNS development, an *Hmx* function that is conserved in *Drosophila* - but it also had effects on the development of the mouse inner ear.

"We didn't expect it to work as well as it did," said Lufkin, adding that these types of experiments have been done in the past, but in many cases, the proteins failed to rescue nonevolutionary conserved functions. "This demonstrates, at least in the case of this one gene, that all the functional domains are still there, and implies that it is through expression that [*Hmx*] has been evolutionary selected," Lufkin told us.

This addresses a very important evolutionary question, "the use of old genes for new purposes," said Mario Capecchi, of the University of Utah, Salt Lake City, who was not involved in the *Developmental Cell* study. "It does not obviate mutations, but places the emphasis on the control of old genes in new contexts, rather than mutations in their protein encoding regions," he said.

"It's impressive work," said Jacqueline Deschamps, of the Netherlands Institute for Developmental Biology, Utrecht, who was also not involved in the *Developmental Cell* study. Deschamps felt that the work by Lufkin and colleagues was nicely complemented by a previous study, which suggested that the regulation of a *Hox* gene, *HoxD*, was coopted when vertebrates acquired novels structures such as limbs.

"These proteins regulate basic conserved processes, such as cell proliferation and survival, so if by accident they are placed under the control of a new regulatory region, and are suddenly expressed, say in the inner ear, they could play a major role in the development there," Deschamps told us. And because

Hmx and *Hox* genes are well-conserved master switches, it is reasonable to discover that the *DHmx* protein supports the development of an organ system that *Drosophila* does not possess, she said.

Overall, Lufkin feels that the acquisition of new contexts for old genes will become a common theme in evolutionary developmental biology - often playfully referred to as 'evodevo.' "As we go forward... we will tend to see that the idea of the cooption of regulatory regions is just as viable a means of selection as the mutation of protein coding sequences," he said.

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