Many a mickle makes a muckle: How changes in animals' size and shape arise

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How does nature's great diversity in the shape and size of organisms evolve? The group of David Stern at Princeton University has managed to show how in fruit flies a gene enhancer can change its function through stepwise changes in DNA sequence to give rise to differences in animals' appearance. Alistair McGregor of the University of Veterinary Medicine, Vienna, contributed to the work, which is published as an article in the current issue of *Nature*.

The transcription of genes is tightly controlled, with a bewildering array of regulatory DNA sequences interacting with a similarly large number of proteins and other factors to determine which genes are active when and where. Understanding how it all works has challenged countless molecular biologists over the past decades but we are now starting to make significant progress. Even so, we have scarcely begun to understand how the entire complexity evolves to give differences in the size and shape of organisms. Exciting new findings are now reported by the group of David Stern at Princeton University, in collaboration with Alistair McGregor of the University of Veterinary Medicine, Vienna and with François Payre of the Université de Toulouse.

Stern's group is investigating the evolution of morphology in fruit flies. The larvae of two closely related flies, the widespread *Drosophila melanogaster* (which appear as if by magic around our fruit bowls in summer) and the more local *Drosophila sechellia* (which is found only on the Seychelles), differ in their patterns of hairs or "trichomes". The difference stems from changes in the expression of the wonderfully named "shaven baby" (svb) gene: svb is not expressed in certain types of cells in *Drosophila sechellia* and as a result their larvae lack lawns of hairs on the tops and sides of their backs.

Previous work in Stern's group had determined that differences in the DNA sequence of the svb regulatory region caused the difference between the hairy and naked species. McGregor found that particular regions of the so-called enhancer E were responsible for controlling expression of the svb gene on the top and sides of fly larvae. The sequence of E6, the part of the enhancer that activates the gene, is subtly different in *Drosophila sechellia* compared with other related species and two post-docs in Stern's lab, Nicolás Frankel and Deniz F. Erezyilmaz, have now systematically examined the effects of each of the changes in isolation and together.

The results provide an elegant demonstration of evolution in action. At least five changes were found to contribute to the altered functional properties of the enhancer. Interestingly, none of the changes on its own has a particularly dramatic effect and the effect of all the changes together is far greater than the sums of all the individual effects. In other words, the effect of any particular change depends on what changes may already be present.

As McGregor notes, the experiments reported in the current issue of *Nature* represent "one of the first functional dissections of the contribution of individual nucleotide changes in an enhancer responsible for morphological evolution." The results provide a possible explanation for how individual mutations, each with relatively minor consequences, can be "fixed" in a population as a result of subsequent events, leading ultimately to the evolution of distinct morphologies.

McGregor has now left Vienna for Oxford Brookes University (UK), where he is continuing his study of the evolution of animal development and morphology.

More information: Morphological evolution caused by many subtle-effect substitutions in regulatory DNA by Nicolás Frankel, Deniz F. Erezyilmaz, Alistair P. McGregor, Shu Wang, François Payre and David L. Stern is published in the current issue of *Nature* (Vol. 474, pp. 598-603). www.nature.com/nature/journal/ … ull/nature10200.html

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