

NEWS RELEASE

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NC State Geneticists Show Ripple Effects of Gene Mutations

FOR IMMEDIATE RELEASE

When a plane arrives late to an airport, it affects more than just the frustrated passengers on the tardy plane – the ripple effects could throw the entire day’s timetable off schedule.

Similarly, in a new study, North Carolina State University geneticists have found that changes to genes regulating olfactory behavior in the fruit fly *Drosophila melanogaster*, a popular insect model for genetics, have far greater implications than previously appreciated.

The study is presented in a paper published in the Sept. 7 online edition of *Nature Genetics*.

Dr. Robert Anholt, professor of zoology and genetics, director of NC State’s Keck Center for Behavioral Biology and the paper’s lead author, said that in the study of how genes affect behavior, the days of thinking about genes in a linear fashion are over.

“In the past, scientists would make a mutation – or a change in the genetic information – in a gene, observe the effect on behavior and say that the particular gene is essential for a particular behavior,” he said. “But when you perturb a gene, you do not just perturb a gene. You create, instead, an effect like the ripples produced when you throw a pebble into a pond. We need to think in terms of networks that generate behavior.”

The study breaks new ground because it enabled the scientists to quantify the extent of the ripples in the genome that affect behavior, Anholt said.

In previous studies, the scientists introduced little pieces of DNA, or transposons, randomly into the genome. “If the transposons insert in a regulatory region of a gene, or inside a gene, they disrupt the function of the gene,” Anholt said.

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Anholt's lab studied olfactory behavior because it can be readily measured and is essential for survival. The investigators isolated a series of smell-impaired flies that were genetically identical but with one particular disrupted gene, and showed enhanced effects when these genes interacted.

"We were able to place them into a network of genetic interactions which provided us with a little view of how genes might work together to determine behavior. Imagine that you are putting together pieces of a puzzle and there comes a moment when you get an inkling of what the final picture might look like," Anholt said.

In the study published in *Nature Genetics*, the scientists took five genes involved in olfactory behavior in *Drosophila melanogaster*, extracted the RNA from these five lines and compared their transcriptomes, or all the RNA, of males and females separately. It was important for this study to use a model organism that can be highly inbred so that all individuals are genetically identical. Equally important was the use of sophisticated statistical analyses applied by study co-author Dr. Trudy Mackay, William Neal Reynolds professor of genetics at NC State.

"If we make a perturbation in one gene by introducing a transposon, what happens to the rest of the transcriptome? That's the question we asked," Anholt said. "It turns out that the genomic perturbations arising from a single insertion are substantial. With this experiment, we could see how many genes were perturbed when we mutated one gene, but we could also look at the overlap of the ripples."

In addition, the researchers were able to identify the numbers of male- or female-specific genes that were affected.

Finally, in what Anholt called the "tour de force" of the study, the researchers attempted to find whether genes in the ripples actually affect olfactory behavior.

To address the issue, the researchers went to the *Drosophila* stock center and its collection of mutants and used a genetic method, pioneered by Mackay, called quantitative complementation tests.

"Two-thirds of the genes within ripples resulting from the smell-impaired mutations themselves affected olfactory behavior. This means that the interactions that we see in the transcriptome mirror the genetic interactions that we see at the behavioral level. It also shows that this approach is a very good strategy for large-scale gene discovery for behavior."

Anholt says this approach can be applied to any complex trait in any animal with a controlled genetic background.

"In the end, we're trying to find how subtle variations in genes affect behavior, and how genetic networks change in response to the environment and during development and evolution," he said.

The study was done in collaboration with Syngenta's Torrey Mesa Research Institute, and the W.M. Keck Foundation and the National Institutes of Health supported the research.

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Note to editors: An abstract of the paper follows.

The Genetic Architecture of Odor-Guided Behavior in *Drosophila*: Epistasis and the Transcriptome

Authors: Robert R.H. Anholt, Trudy F.C. Mackay, Christy Dilda, Nalini Kulkarni, Indrani Ganguly, Stephanie Rollmann, North Carolina State University; Sherman Chang, Kim Kamdar, Torrey Mesa Research Institute; Juan-Jose Fanara, University of Buenos Aires

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Abstract: We combined transcriptional profiling and quantitative genetic analysis to elucidate the genetic architecture of olfactory behavior in *Drosophila melanogaster*. We applied whole-genome expression analysis to five coisogenic smell-impaired (*smi*) mutant lines and their control. We used analysis of variance to partition variation in transcript abundance between males and females and between *smi* genotypes and to determine the genotype-by-sex interaction. A total of 666 genes showed sexual dimorphism in transcript abundance, and 530 genes were coregulated in response to one or more *smi* mutations, showing considerable epistasis at the level of the transcriptome in response to single mutations. Quantitative complementation tests of mutations at these coregulated genes with the *smi* mutations showed that in most cases (67%) epistatic interactions for olfactory behavior mirrored epistasis at the level of transcription, thus identifying new candidate genes regulating olfactory behavior.