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## "Noisy" Genes Can Have Big Impact

Experiments by Howard Hughes Medical Institute (HHMI) researchers have revealed it might be possible for randomness in gene expression to lead to differences in cells—or people, for that matter—that are genetically identical.

The researchers, HHMI investigator Erin K. O'Shea and colleague Jonathan M. Raser, both at the University of California, San Francisco, published their findings May 27, 2004, in *Science Express*, the online edition of the journal *Science*.

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According to O'Shea, the original notion that random noise in gene expression—the processes by which proteins are synthesized from the information contained in DNA—arose from a paradox. "While processes such as gene expression involved in the development of organisms proceed in a very orderly fashion, paradoxically, they depend on chemical reactions that are inherently probabilistic, like flipping a coin," said O'Shea. "And since these processes involve small numbers of molecules, they should be significantly affected by chance, just as flipping a coin a few times will be more heavily affected than flipping it many times."

Earlier experiments by Michael Elowitz, who is now at the California Institute of Technology, and his colleagues at The Rockefeller University demonstrated that this type of random noise existed in the common bacterium *E. coli*. In later experiments, Raser and O'Shea set out to explore the mechanism underlying random noise in gene expression in a higher organism—choosing the most primitive animal, yeast.

Raser and O'Shea used an indicator technique developed by Elowitz to detect noise in gene expression. They engineered yeast cells to produce blue and yellow fluorescent indicator proteins under the control of the same "promoter"—the segment of the gene regulating its expression. In this

scheme, if there were no noise, every cell would appear the same mix of blue and yellow color under the microscope.

However, if any noise crept in, it would produce a variation in colors among the cells. This color variation could then be measured to determine the amount of noise that was present. This method eliminated any influence of external environmental factors or variables such as differences in cell type, since the two genes were operating inside the same cell.

After using this technique to study the function of various promoters, the scientists concluded that noise did, indeed, affect gene expression in the yeast cells. They also found that different promoters produced different amounts of noise.

Based on their studies, Raser and O'Shea believe they have identified the source of a major portion of the random noise they observed. "Our experiments suggest that for the promoters we studied, a major source of noise is the act of preparing the promoter DNA, the regulatory region, to be competent for transcription," said O'Shea. This preparation, she said, involves "remodeling" the protective structure, called the nucleosome, which enfolds the regulatory region of the gene so that the transcription machinery can access it. "And the step that is generating noise is this act of removing the nucleosomes, in order to allow access of the transcription machinery and the regulatory proteins," she said.

Remodeling is particularly slow, O'Shea said, and subject to significant probabilistic variation. This variation would likely have an affect on the amount of mRNA produced for each marker-tagged gene and thus the level of a given protein in the cell—affecting its color.

According to O'Shea, randomness in gene express could have important evolutionary and biological implications, both advantageous for cells and deleterious. For example, mutations in genes could change their "noisiness" independent of the effect of the mutation itself. Noise in essential genes could be deleterious for a cell. However, noise could also produce diversity in populations of cells with the same genetic makeup, and this diversity could make them more adaptable to changes.

Another effect of randomness in gene expression might be observed, for example, in cells with two slightly different copies of the same gene, where one might be noisier than the other. Such noise might also produce variability among cells that might offer evolutionary advantages.

Noise in genes might also be a trigger for the formation of tumors, said O'Shea. In cases where cells lose one copy of a gene through mutation, the reduction in gene number increases the noise in gene expression. This increase in noise makes it more likely that the remaining gene might alter its activity to trigger uncontrolled proliferation.

Noise could be necessary for normal development of some biological systems, said O'Shea. For example, when olfactory neurons in the developing

embryo are “deciding” which of a multitude of possible odorant receptors they will produce—a choice that is final—random noise in gene expression might be necessary to enable this decision, she said.

O'Shea said that her group plans to continue this line of research and hopes to identify in which cases such randomness is beneficial to an organism. Then, they will alter the level of noise and determine how it affects the fitness of the organism. They also want to follow noise production in a single cell over time—rather than in populations of cells—to explore in more detail how noise is produced.