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Random fluctuations give rise to odd genetic phenomenon

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(PhysOrg.com) -- For years, biologists have wondered how it is possible that not every person who carries a mutated gene expresses the trait or condition associated with the mutation. This common but poorly understood phenomenon, known as incomplete penetrance, exists in a wide range of organisms, including humans.

Many mutations in genes that are linked to diseases, including Parkinson's disease and Type 1 diabetes, are incompletely penetrant. Some of this variation may be due to environmental factors and the influence of other genes, but not all: It has been shown that genetically identical organisms living in the same environment can show variability in some incompletely penetrant traits.

Now, a team of MIT biophysicists has demonstrated that some cases of incomplete penetrance are controlled by random fluctuations in gene expression.

"It's not just nature or nurture," says Alexander van Oudenaarden, leader of the research team and a professor of physics and biology at MIT. "There is a random component to this. Molecules bounce around and find each other probabilistically. It doesn't work like clockwork."

In a study of intestinal development of C. elegans, a small worm, the team was able to pinpoint specific fluctuations that appear to determine whether the mutant trait is expressed or not.

The work, published in *Nature* on Feb. 18, may also be relevant to human diseases that display incomplete penetrance, such as Parkinson's disease and Type 1 diabetes, says van Oudenaarden. For example, knowing the specific points in cellular pathways that are most important in controlling a cell's response to mutation could give drug designers better targets for new therapies.

The team studied the embryonic development of the digestive tract of C. elegans. The tract starts out as a single cell and eventually becomes 20 cells in the adult worm. That process is initiated by a gene called skn-1, which activates a series of other genes. Most of those genes code for transcription factors, which bind to DNA and turn on additional genes.

The team first characterized normal progression of intestine development, using a probe the team members developed that binds to messenger RNA inside cells, allowing them to count the number of copies of a particular messenger RNA sequence. (Messenger RNA carries DNA's instructions to the cell's protein-building machinery.)

They then studied worms with a mutation in skn-1, and found that some

of the worms developed normal digestive tracts while others failed to develop a digestive tract. It appears that the controlling factor is the number of copies of mRNA produced by a gene called end-1, one of the genes activated by skn-1. The number of end-1 mRNA strands varied greatly in embryos with the mutation: In those with a number above a certain threshold, development proceeded normally; if the number was below the threshold, no digestive tract developed.

It appears that evolution has produced networks of genes that smooth out the effects of those fluctuations, which are revealed only when there is a mutation in the pathway, says van Oudenaarden.
Van Oudenaarden plans to use the same technique to study mammalian colon stem cells, in hopes of figuring out whether random fluctuations in gene expression influence the mutations that can cause cancer. If he can show that random fluctuations in a particular gene appear to be subject to the same threshold effect that he saw in C. elegans embryonic development, it could give drug designers new targets.

More information: "Variability in gene expression underlies incomplete penetrance in multicellular development," Arjun Raj, Scott Rifkin, Erik Andersen, Alexander van Oudenaarden. Nature, February 18, 2010.

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