Rare evolutionary event detected in the lab

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It took nearly a half trillion tries before researchers at The University of Texas at Austin witnessed a rare event and perhaps solved an evolutionary puzzle about how introns, non-coding sequences of DNA located within genes, multiply in a genome. The results, published today in the *Proceedings of the National Academy of Sciences*, address fundamental questions about the evolution of new species and could expand our understanding of gene expression and the causes of diseases such as cancer.

"Until now, the only way researchers could track the evolution of introns was through phylogenetic analysis which is examining the evolutionary relationships among sets of related organisms," says Scott Stevens, associate professor of Molecular Biosciences. "Our work is the first experimental verification that shows how introns can be transposed into an organism."

For a long time, scientists have known that much of the DNA within any given organism's genome does not code for functional molecules or protein. However, recent research has found that these genetic sequences, misnamed "junk" DNA in the past, often do have functional significance.

These introns are no exception. Now known to play a role in which genes are expressed, introns are the portion of gene sequences that are removed or spliced out of RNA before genes are translated into protein. When eukaryotes first diverged from bacteria, there was a massive invasion of introns into the genome. All living eukaryotes—from yeast

to mammals—share this common ancestor, and while simpler organisms like yeast have eliminated most of their introns, organisms such as mammals have considerably expanded their intron inventory. Humans have over 200,000 introns which take up about 40 percent of the genome.

In the current paper, Stevens and his co-author, Sujin Lee, a former graduate student in cellular and molecular biology at UT Austin, used a new reporter assay to directly detect the loss and gain of introns in budding yeast (Saccharomyces cerevisiae). The team tested nearly a half trillion yeast and found only two instances where an intron was added to a new gene. The proposed mechanism for this addition is a reversal of a splicing reaction.

Normally, to make proteins, RNA reads instructions from DNA, skipping the code contained in the introns. But in these two instances, the cell read the DNA in reverse and allowed the introns to make it into the RNA, thus creating a permanent genetic change. These are called intron gains, and if these accumulate over time, they can contribute to the development of new species as well as human disease.

"We showed in this project that introns continue to be gained, although infrequently at any point in time," says Stevens. "But can introns drive evolution? If these sequences give organisms a selective advantage and become fixed in a population, others have shown that it can be a major factor in the creation of new species."

These evolutionary advances come at a cost, however, because diseases such as cancer correlate with the improper removal of introns from RNA. Stevens adds, "We are continuing this work to further understand how this process impacts our genetic history, our future, and the prospects of curing disease."

More information: Spliceosomal intronogenesis, *PNAS*, www.pnas.org/cgi/doi/10.1073/pnas.1605113113

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