

New study of gene evolution could lead to better understanding of neurodegenerative disease

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Genetic evolution is strongly shaped by genes' efforts to prevent or tolerate errors in the production of proteins, scientists at The University of Texas at Austin and Harvard University have found.

Their study also suggests that the cost of errors in protein production may lie in the malformed proteins themselves, rather than in the loss of functional proteins. Misfolded proteins can build up in long-lived cells, like neurons, and cause neurodegenerative diseases.

The work, by Claus Wilke at The University of Texas at Austin and D. Allan Drummond at Harvard, is described in the July 25 issue of the journal *Cell*.

"It has long been believed that the main force of natural selection on protein-coding genes is the need to maintain a working protein," says Drummond, a Bauer Fellow in Harvard's FAS Center for Systems Biology. "Our work suggests that another force may be equally important: the need to avoid misfolded proteins resulting from errors in translation."

Wilke says the study may lead to better ways to detect genes with mutations that lead to production of toxic, misfolded proteins, and ultimately, to a better understanding of neurodegenerative disease.

"These genes may produce proteins that look innocuous but nevertheless cause a severe disease condition," says Wilke, assistant professor of integrative biology.

Protein molecules must fold to become biologically active, and mistakes can cause misfolding, which can be toxic. Yet the protein-producing factories in our cells are estimated to make mistakes in 20 percent of the molecules they produce. Adaptations to this surprising sloppiness may be crucial in understanding the evolution of genes across species, from bacteria to humans, say Wilke and Drummond.

Essentially, they write, natural selection has fostered the evolution of genes that minimize the effects of errors in translation, the production of proteins from genetic templates in cells. An example is the careful placement of codons, which are sections of DNA that code for amino acids, the building blocks of proteins. Some codons translate more accurately, and previous research had suggested that high-fidelity codons are positioned at key locations in the genome, where a mistake might be harmful. These studies, however, had only considered fast-growing organisms like *E. coli* bacteria and fruit flies.

"Contrary to what was believed, our work shows that even in the human genome, codons are positioned to minimize errors," says Wilke. "Just like a mistake on your taxes is more costly than a mistake on your grocery list—so you concentrate more on your taxes—cells seem to concentrate on preventing mistakes that might result in costly misfolded proteins."

Wilke and Drummond analyzed humans, mice, fruit flies, worms, yeast and *E. coli* bacteria and discovered all of these organisms have evolved ways to prevent the production of costly aberrant proteins.

"Finding such sweeping effects from a single, simple cost has the

potential to reshape the way evolution is studied at the molecular level," Drummond says. "While much work has focused on how evolution makes creatures different, our work emphasizes fundamental ways in which all life is the same."

While evolutionary studies are often retrospective, Wilke and Drummond also developed a molecular-level evolutionary simulation, allowing them to track the evolution of genomes encoding many simple proteins over millions of generations. In some simulations, they added evolutionary costs for misfolded proteins, while in others this cost was not factored in. They found that genomes evolving with misfolding costs developed all the genome-wide patterns seen in real organisms, while those evolving without costs did not.

The work could have long-term implications for our understanding of neurodegenerative diseases.

Misfolded proteins are known to accumulate in neurons and are central players in fatal disorders such as amyotrophic lateral sclerosis (ALS), better known as Lou Gehrig's disease. Wilke and Drummond suggest that mistranslation may contribute to long-studied forms of ALS and other similar diseases.

Source: University of Texas at Austin

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