Preventing dangerous nonsense in human gene expression

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Human genes are preferentially encoded by codons that are less likely to be mistranscribed (or "misread") into a STOP codon. This finding by Brian Cusack and colleagues from the Max Planck Institute for Molecular Genetics in Berlin and the CNRS in Lyon and Paris is published in the open-access journal *PLoS Genetics* on October 13th, 2011.

Since the completion of the human genome sequence over a decade ago, a multitude of studies have investigated the forces that have shaped the genome over time. However, because gene expression errors are not inherited, they have been disregarded as an evolutionary force until now.

In biological systems, mistakes are made because the cellular machinery is complex and error prone. The errors made in copying DNA for transmission to offspring (genetic mutations) have so far been the primary focus of molecular evolution. But errors are much more frequent in the day-to-day task of gene expression, for example in the transcription of DNA into RNA. This study shows how human genes use a dual strategy of "prevention and cure" to deal with a specific type of gene expression error: transcriptional errors that create premature STOP codons (so-called "nonsense errors"). Nonsense errors can be highly toxic for the cell, so natural selection has evolved a strategy called nonsense-mediated decay (NMD) to "cure" such errors. However, this cure is inefficient. This work identifies a strategy of prevention that has evolved to compensate for the inefficiency of NMD by decreasing the frequency of nonsense errors. Natural selection achieves this through the

avoidance of codons that are prone to nonsense errors and the preferential usage of codons robust to such errors.

Cusack et al's results provide a rationale for the evolution of robustness by implying that transcriptional errors are visible to natural selection because they are frequent and deleterious. According to the authors, "this raises the question of the past and present impact of such errors on human disease." An accompanying Perspectives article is published in PLoS Genetics on the same day.

More information: Cusack BP, Arndt PF, Duret L, Crollius HR (2011) Preventing Dangerous Nonsense: Selection for Robustness to Transcriptional Error in Human Genes. PLoS Genet 7(10): e1002276. doi:10.1371/journal.pgen.1002276