

Spelling mutations and evolutionary advantages

March 18 2016

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Different people sometimes spell the same word differently - organisation versus organization, or analogue versus analog. In such words, despite the variation in the strings of letters, the meaning conveyed by the alternatives remains the same. Similarly, DNA codes carrying instructions for creating a protein can sometimes be 'spelt' differently, although they specify the exact same sequence information to create that protein. Until recently, most biologists believed that mutations that created such 'synonymous' DNA codes, had very weak effects on the evolution of organisms. However, a new study by an international team of scientists, including those from the National Centre for Biological Sciences (NCBS), Bangalore, shows that a different set of DNA codes specifying the same product can have major effects on the survival and evolution of living beings.

The code of life - composed of triplet codons of the four DNA alphabets A, T, G and C - is quite redundant. For example, the amino acid Alanine, is specified by no less than four alternative triplet codes (GCT, GCC, GCA and GCG), or codons. This redundancy is at the root of what molecular biologists term 'synonymous mutations', where a change in the

DNA sequence of a gene does not change the sequence of the protein it codes for. Mutations resulting in changes to protein sequences are expected to cause disruptions in function, and are hence likely to affect an organism's abilities or fitness. Contrary to this, synonymous mutations have been generally ignored in this context. Deepa Agashe at NCBS and her team of collaborators have reinforced a growing body of evidence that synonymous variants of a gene affect an organism's fitness. Moreover, they have now shown that single highly beneficial synonymous mutations can allow organisms to rapidly evolve and adapt to their environment.

Working on the bacterium *Methylobacterium extorquens*, the group created several variants of a gene called *fae*. This gene codes for a metabolic enzyme essential for survival and growth in an environment where the only source of carbon comes from methanol or methylamine. Under such restrictive conditions, bacteria undergo strong selection for retaining the *fae* gene function. When grown in conditions where methanol was provided as the sole carbon source, all [bacterial populations](#) with the 'synonymous' *fae* gene variants performed poorly when compared to bacteria carrying the normal gene.

However, when bacterial populations carrying these variants of *fae* were grown over a long period of time with methanol being the only carbon source - described as 'strong selection conditions', an interesting phenomenon was observed. Within 100 - 200 generations, these bacterial populations began to regain their fitness through additional mutations to the gene variants. Many of these mutations were again synonymous. Furthermore, these mutations occurred at single points within the gene, were highly beneficial, and they seemed to recur in multiple experiments. "What is surprising about our results is that the beneficial mutations we see are highly repeatable in specific gene variants - you can think of this process with an analogy to climbers - different climbers who start independently from the bottom of a hill are using the exact

same strategy to reach the top!", says Deepa Agashe, the lead author of the publication detailing these findings.

Studies like the one described here are critical in understanding the genetic basis of adaptation. Understanding adaptation, in turn, is the key to comprehending evolution and for predicting future dynamics of populations. For example, being able to forecast the development of antibiotic resistance through genetic mutations in a bacterial population would help in developing better drugs for diseases. Until now, synonymous mutations and gene variants were considered relatively unimportant for such studies on adaptation, due to a lack of information about their effects on organism fitness. This study reinforces the view that such synonymity can no longer be ignored as irrelevant in the processes of adaptation and evolution.

More information: Deepa Agashe et al. Large-effect beneficial synonymous mutations mediate rapid and parallel adaptation in a bacterium, *Molecular Biology and Evolution* (2016). [DOI: 10.1093/molbev/msw035](https://doi.org/10.1093/molbev/msw035)

Provided by National Centre for Biological Sciences

Citation: Spelling mutations and evolutionary advantages (2016, March 18) retrieved 26 June 2024 from <https://phys.org/news/2016-03-mutations-evolutionary-advantages.html>

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