Evolution silences harmful mutations

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A depiction of the double helical structure of DNA. Its four coding units (A, T, C, G) are color-coded in pink, orange, purple and yellow. Credit: NHGRI

Sometimes so-called synonymous mutations occur in DNA. These do not lead to a change in the protein sequence but which may still have major

negative effects on the ability of bacteria to survive. New research from Uppsala University has now shown that an organism can efficiently compensate for the negative effects. These findings have been published in the journal *Molecular Biology and Evolution*.

For a long time it has been believed that synonymous mutations are 'silent', i.e. that they have no effect - positive or negative - on the gene product (protein) or on the growth and survival of the organism. However, in recent years several studies have shown that these mutations still often cause problems for the organism even though they do not change the protein sequence.

"An important question for evolutionary biologists and geneticists is therefore why these mutations have a negative effect. Our study shows why they are deleterious and how efficiently and rapidly a bacterium can genetically compensate for the negative effects of such mutations by means of additional new mutations," says Dan I. Andersson, senior author of the study.

For the present study, researchers looked more closely at four synonymous but costly mutations in the gene for a ribosomal protein. They observed that the main problem with these mutations was that they caused a decrease in production of the mutated ribosomal protein. The cells entered into a vicious circle in which low protein levels resulted in defective ribosomes that in turn caused further problems with protein synthesis. By allowing these low fitness bacteria to grow for many generations it was possible to see that evolution solved the problem of synonymous mutations by creating compensatory mutations that restored the level of ribosomal protein to normal. In this way, the researchers have gained a greater understanding of why silent mutations might reduce fitness was and how bacteria could compensate for them.

"It is probably possible to find similar effects of 'silent' mutations in

many other genes and organisms, especially in the genes which code for proteins which participate in the cell's central information flow," says Anna Knöppel, a doctoral student at the Department of Medical Biochemistry and Microbiology at Uppsala University.

More information: Anna Knöppel et al. Compensating the fitness costs of synonymous mutations, *Molecular Biology and Evolution* (2016). DOI: 10.1093/molbev/msw028

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