GENETIC VARIATION

Synonymous mutations break their silence

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URLs

Entrez gene:
MDR1
http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=gene&cmd=Retrieve&dopt=full_report&list_uids=5243

The degeneracy of the genetic code means that many mutations in coding sequences, especially at the third base of codons, do not affect protein sequence and are therefore considered silent. However, there is increasing evidence that they could still have effects on transcription, splicing, mRNA transport or translation, any of which could alter the phenotype. New research shows that a synonymous polymorphism that is part of a common haplotype in humans affects the function of the encoded protein by altering its structure.

Kimchi-Sarfaty *et al.* looked for phenotypic effects of a synonymous polymorphism in a common haplotype in the multidrug resistance 1 (*MDR1*) gene, which encodes P-glycoprotein, by expressing it in cell lines. The synonymous variant altered the effectiveness of inhibitors of P-glycoprotein. The mRNA levels were not altered by the mutation, implying that its effect was not at the level of transcription. On the other hand, the effect was enhanced by increasing the concentration of the transgene, implying that an increase in the amount of mRNA that is available to the translation machinery might be causative. The authors therefore reasoned that differences in tRNA abundance underlie the variation. This is consistent with the fact that the variant uses a codon that is rarer than the wild type. As further evidence for this, the authors created a variant that uses an even rarer codon, and found an even greater phenotypic effect.

The authors suggest that the need for rare tRNAs to translate rare codons slows down translation and causes the protein to fold into a different structure. In support of this theory, the conformation-sensitive antibody binding and trypsin susceptibility of the variant were found to be different from the wild-type protein.

These results show that a common human polymorphism, that might be assumed to be silent, has phenotypic effects in a clinically important protein. The phenomenon of non-silent synonymous mutations is therefore of interest not only to evolutionary biologists. Many of the synonymous polymorphisms in the accumulating body of SNP data might turn out to have important phenotypic consequences.

Patrick Goymer

ORIGINAL RESEARCH PAPER Kimchi-Sarfaty, C. *et al.* A 'silent' polymorphism in the *MDR1* gene changes substrate specificity. *Science* 21 December 2006 (doi:10.1126/science.1135308)
FURTHER READING Chamary, J. V., Parmley, J. L. & Hurst, L. D. Hearing silence: non-neutral evolution at synonymous sites in mammals. *Nature Rev. Genet.* **7**, 98–108 (2006)