

PublisherInfo		
PublisherName	:	BioMed Central
PublisherLocation	:	London
PublisherImprintName	:	BioMed Central

Yeast fitness and protein evolution

ArticleInfo		
ArticleID	:	3942
ArticleDOI	:	10.1186/gb-2001-2-9-reports0030
ArticleCitationID	:	reports0030
ArticleSequenceNumber	:	20
ArticleCategory	:	Paper report
ArticleFirstPage	:	1
ArticleLastPage	:	3
ArticleHistory	:	RegistrationDate : 2001-7-5 Received : 2001-7-5 OnlineDate : 2001-8-17
ArticleCopyright	:	BioMed Central Ltd2001
ArticleGrants	:	

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Abstract

The impact on fitness of homozygous deletions in yeast has been shown to correlate with the rate of protein evolution assessed as the evolutionary distance between yeast and *Caenorhabditis elegans*.

Significance and context

It seems intuitive that relatively dispensable proteins should undergo weaker purifying selection than proteins that are essential and might, therefore, accumulate mildly deleterious mutations. This prediction has been difficult to confirm, however, and there is even evidence from a study in mouse that seems to refute this hypothesis. Hirsh and Fraser have used data produced by a high-throughput parallel analysis using yeast deletion mutants to investigate the link between protein dispensability and evolutionary rate. In the parallel genomic study, homozygous deletant yeast strains - each assigned a unique genetic 'barcode' detectable by hybridization on a DNA chip - were grown in batch culture. The relative rate of growth of each mutant - a measure of fitness - was estimated from the relative fluorescence intensities of the barcode signals. The authors calculate the fitness effect (f_i) of the deletion as $1 - r_i/r_{\max}$, where r_i and r_{\max} are the growth rate for the gene i deletant and maximal growth present in the culture, respectively. The values of f_i range from 0 (for a completely dispensable gene) to 1 (for an essential gene). To estimate the relative rate of evolution of yeast proteins, they compared the relevant yeast proteins with the corresponding orthologs from *C. elegans*, having ensured that the orthologous sequences had been evolving separately after the Fungi-Animalia split.

Key results

Hirsh and Fraser obtained reliable estimates of fitness for 548 homozygous single-gene deletants. The evolutionary distances d_i (number of substitutions per amino acid site) could be estimated for 119 mutants out of the 548 using two different methods. They found a statistically significant relationship between d_i and f_i , showing that proteins with a lower fitness effect are more divergent. But, the d_i values represent evolutionary change not only in the yeast sequences but also in the corresponding nematode orthologs. To estimate evolutionary change only in the lineage leading to yeast, d_i measures were split into two components, one between yeast and the hypothetical most recent common ancestor (MRCA) of fungi and animals and another between the MRCA and *C. elegans*: the outgroup sequences were orthologs present in other completely sequenced genomes. Hirsh and Fraser analyzed 48 yeast proteins

in this way and again a significant relationship between f_i and the 'new' d_i values was obtained. Most interestingly, statistically significant results were obtained when they plotted f_i (from yeast) against the d_i between the MRCA and the nematode. This suggests that non-essential proteins that have an impact on the fitness of yeast might also have a proportional effect on worm fitness. No differences were detected when the essential genes were subject to the same analysis and compared with the non-essential ones, which is consistent with the results of analyses in mouse. When the comparison was carried out against the most dispensable 60 proteins (smallest f_i values), however, a highly significant difference was detected.

Reporter's comments

This work provides the long awaited (at least preliminary) confirmation of a fundamental prediction about protein evolution. It is an example of how genomic data can be exploited from different perspectives to address important biological questions. In fact, the starting point of the present study was the results of a high-throughput parallel analysis of yeast deletants published almost two years ago within the framework of a 'pure' functional genomics project. Now the data have been used to test an evolutionary hypothesis. The availability of the complete genomic sequences of the worm and of a panoply of prokaryotes certainly simplified the work and allowed the detection of a sufficient number of orthologous sequences for the results to be analyzed statistically. Similar projects may be carried out soon for the worm as projects of systematic inactivation of the nematode genes are already yielding results.

Table of links

[Nature](#)

References

1. Hirsh AE, Fraser HB: Protein dispensability and rate of evolution. *Nature*. 2001, 411: 1046-1049. 0028-0836