

## MOLECULAR EVOLUTION

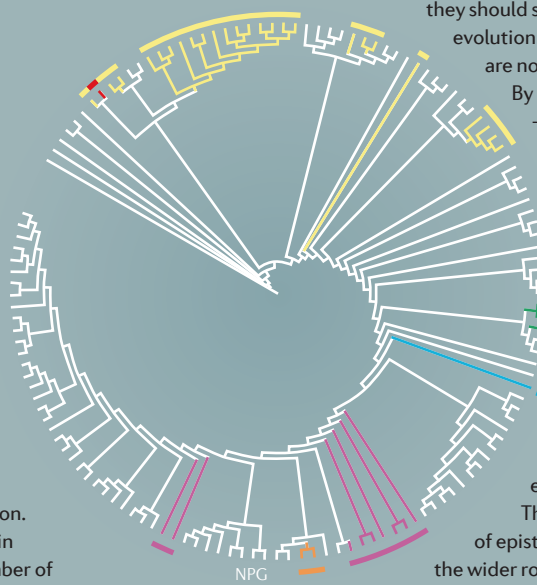
## Epistasis prevails

Multiple forces are proposed to determine the likelihood of fixation of an amino acid change through evolution. A recent study of over 1,000 orthologues of 16 proteins has enabled a quantitative investigation of the relative contributions of various forces during long-term evolution. Amino acid substitutions were found to be primarily constrained by the genetic background in which they occurred. Thus, there is a central role for epistasis in long-term molecular evolution, such that an amino acid substitution may be beneficial in one organism but deleterious in other.

Breen *et al.* aligned the orthologous sequences of 16 of some of the most widely sequenced genes (for both organelle- and nuclear-encoded proteins) from over 1,000 metazoans. They analysed the number of different amino acids that were present in orthologous positions and found the average to be eight; thus, typically

two-fifths (40%) of the twenty potential amino acids are acceptable at each amino acid site. If there is no epistasis, then an amino acid substitution that is accepted in one species should be equally acceptable in another species at the orthologous position. Epistasis would result in a reduction in the number of potential amino acids accepted at that site, as some substitutions would have deleterious effects owing to interactions with the genetic background.

As the authors observed that 40% of the amino acids are acceptable at each position over long-term evolution, in the absence of an epistatic influence



they should see that over short-term evolution 40% of all substitutions are not prevented by selection. By analysing the dN/dS ratios — a measure of amino acid substitution — at orthologous sites, Breen *et al.* found that in fact more than 90% of all substitutions are prevented from occurring by selection. Therefore, they were able to conclude that epistasis is a major contributor to long-term molecular evolution.

This finding of the prevalence of epistasis poses questions about the wider roles of epistatic interactions, for example whether they are involved in disease phenotypes.

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**ORIGINAL RESEARCH PAPER** Breen, M. S. *et al.*  
Epistasis as the primary factor in molecular evolution. *Nature* 14 Oct 2012 (doi:10.1038/nature11510)