

Pervasive epistatic interactions between nearby sites in coding and non-coding sequences of *D. melanogaster*

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Abstract

*Most models of sequence evolution assume independence of mutations at different sites; however, there are multiple possible reasons for deviations from independence. In particular, epistatic interactions between sites may lead to non-independence of SNPs and of nucleotide replacements at distinct sites. Here, we show that epistatic interactions between nearby (at distances of up to 5 bp) nucleotide sites shape the patterns of polymorphism and divergence in coding (CDS) and noncoding (NDS) DNA sequences of *D. melanogaster*. Both in within-species polymorphism and in interspecies divergence, the clustering of SNPs and substitutions at nearby sites is positively correlated with the degree of conservatism of the sequence segment. Moreover, clustering of substitutions in the same of the two evolving lineages, suggestive of positive selection or epistatic interactions (Bazykin et al. Nature 2004 Jun 3; 429:558-562), is twice as strong in the conserved regions of NDS, and 3 times as strong in the conserved regions of CDS, compared to the corresponding non-conserved regions. These results show that epistatic interactions between nearby CDS and NDS sites are prevalent genome-wide, and may be an underappreciated contributor to sequence evolution.*