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EVOLUTION

Duplicate gene co-regulation slows evolution

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Gene duplications can drive evolutionary processes and contribute to the development of new biological functions. In mammals, however, new gene duplicates are often degraded into non-functional pseudogenes. Now, researchers from Stanford University describe the evolutionary forces that control the fate of young gene duplicates and the processes that contribute to the long-term survival in some duplicate pairs.

By first analysing RNA sequencing (RNA-seq) data from 46 human tissues and replicating their findings in 26 mouse tissues, the team sought to identify whether the survival of duplicate genes in the mammalian genome is due to subfunctionalization (in which each gene retains a part of the ancestral gene's function) and neofunctionalization (in which one gene takes on a new function after the duplication event), or whether gene dosage-sharing models can better explain the persistence of gene duplicates.

A total of 1,444 duplicate gene pairs were identified in the human genome and then classified according to their co-expression patterns. A gene pair was classified as possibly subfunctionalized or neofunctionalized if each gene was significantly more highly expressed than the other in at least one tissue. Very few duplicate pairs showed evidence of subfunctionalization or neofunctionalization, and most of these arose from duplication events dating before the emergence of placental mammals. The few genes that were identified as potentially subfunctionalized or neofunctionalized, however, displayed characteristic differences (putatively subfunctionalized genes, for example, contained a high number of rare variants, possibly owing to selective constraint).

Overall, the results showed that subfunctionalization of gene expression evolved slowly. But, notably, rates of subfunctionalization and neofunctionalization were higher for duplicate genes located on different chromosomes than for those located close together on the same chromosome (so-called tandem duplicates). Compared with a pair of unrelated genes in close proximity on the same chromosome, tandem duplicates showed more highly correlated gene expression, and shared a greater number of expression quantitative trait loci (eQTLs). Whole-genome chromosome conformation capture (Hi-C) demonstrated higher connectivity (especially promoter–promoter links) of tandem duplicates than between singleton genes. By contrast, Hi-C showed no evidence of linkage between duplicates on different chromosomes. The authors hypothesize that tandem duplicates are highly co-regulated and that the process of genomic separation is important for enabling independent evolution.

Using RNA-seq data from six human and macaque tissues, the researchers analysed the expression levels of young gene duplicates that arose since the human–macaque evolutionary split. They found that human copies usually evolve reduced expression (with the average summed expression in the human duplicates similar to that of the singleton orthologues in the macaque). They propose that downregulation first achieves dosage balance between tandem duplicates and enables early survival of both genes. If a balance is achieved, the expression levels then evolve slowly, owing to constraints on their combined expression. However, if genomic separation occurs, the duplicate genes are able to evolve independently, resulting in long-term persistence and potentially "true functional differentiation".

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