

 STATISTICAL GENETICS

Pleiotropy revisited

Pleiotropy has a fundamental function in biology, and several theoretical models have been developed to explain its role in organismal complexity and evolution. Like many theories, this one has now been put under empirical scrutiny thanks to large-scale data sets. A study of hundreds of mouse, nematode and yeast mutants has revealed some surprises about the genome-wide patterns of pleiotropy and, contrary to expectation, has shown that intermediate levels of pleiotropy promote rather than hinder adaptation.

The data consist of five existing collections of single-gene mutants, knockouts and knockdowns and phenotypic information recorded in the scientific literature (three yeast data sets and one each for mice and worms). The analysis of thousands of gene–trait relationships showed that genomic pleiotropy is actually quite low, as most genes affect only a small (median = 1–7) number of traits. This

is contrary to the long-held assumption that each gene affects every trait. Furthermore, the gene–trait networks show a highly modular architecture: links between traits and genes within a set are more frequent than links outside the set. Modularity was an expected feature of pleiotropy but this property does not appear often in theoretical models. The conclusions above are consistent across five phenotypic data sets and are robust to reductions of up to 90% in the number of traits — the observed patterns should therefore hold even at substantially larger sample sizes and trait numbers.

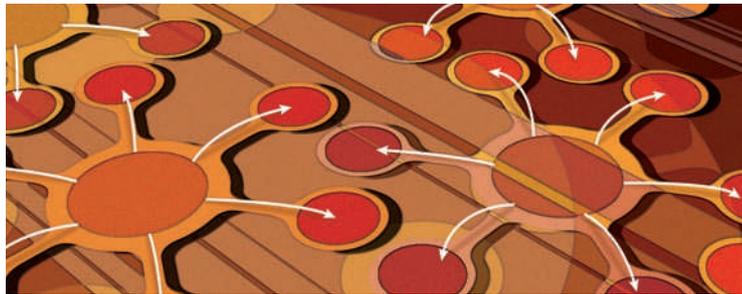
One data set made it possible to establish quantitative relationships between individual mutations and phenotypes and thus to measure the strength of the effect of a gene mutation on a trait. This assessment showed that the magnitude of the effect of a gene on different traits is almost normally distributed, which

suggests, counter-intuitively, that genes that affect the most traits also have a larger effect on each trait.

Theoretical models have assumed that because complex organisms have a higher degree of pleiotropy they also bear a disproportionately high cost of mutation. This has led to the puzzling conclusion that organisms with higher levels of complexity would find it difficult to evolve compared with simpler organisms. The current study proposes a way out of this conundrum: if pleiotropy is low, then mutations are less costly to the organism than expected, and high modularity would contain the effects of any new mutation. The authors also show that the parameter that relates the total effect-size of a mutation to the degree of pleiotropy is optimal at intermediate degrees of complexity: adaptation is therefore more rapid than expected, particularly when it occurs in a relatively complex organism.

Large-scale empirical data are putting flesh on the bones of long-standing theoretical models and, as in this case, they are suggesting wholesale revisions of the overall skeleton.

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