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GENETIC SCREENS

A global map of genetic interactions

Functional interactions between genes can reveal gene roles and interdependencies, but comprehensive studies are a major undertaking owing to the combinatorial complexity of generating double mutants for each pairwise interaction tested. A new large-scale study analyses >23 million double-mutant yeast strains to generate a multilayered map of cellular function.

Costanzo *et al.* used *Saccharomyces cerevisiae* synthetic genetic array technology, in which libraries of single mutants are crossed to generate a double-mutant library. Such approaches have been previously reported on a smaller scale, but here the investigators sought a comprehensive investigation of interactions. Overall, 5,416 genes (>90% of *S. cerevisiae* genes) were combined into a library of >23 million double-mutant strains. To circumvent lethality for essential-gene mutants, they used temperature-sensitive allele strains grown at semi-permissive temperatures.

Using growth rate as a measure of fitness, the authors identified genetic interactions on the basis of whether the fitness of the double mutant deviated from what is expected from multiplicative effects of the single mutants. Overall, they identified ~550,000 negative genetic interactions (fitness lower than expected) and ~350,000 positive genetic interactions (fitness greater than expected).

The catalogue of genetic interactions enabled the construction of a functional map of the cell. Assembling genes into clusters according to the degree of similarity of interaction profiles revealed hierarchical functions. Genes were most closely clustered with those for which the encoded proteins share focused pathways or macromolecular complexes. Zooming out, the clusters grouped together into broader 'bioprocesses' such as vesicle trafficking or cytokinesis, and these were further grouped into the overall cellular compartments in which these processes occur.

This information on both fine-grained and broad aspects of gene function can be leveraged to infer functions of poorly characterized genes. For example, the authors renamed the previously uncharacterized essential gene *YJR141W* as important for cleavage and polyadenylation 1 (*IPA1*) based on its genetic interaction similarity to other mRNA cleavage and polyadenylation factors.

Reflecting important and non-redundant functions, essential genes had approximately fivefold more genetic interactions than non-essential genes and formed the major scaffold of the overall global genetic network. More generally, hub genes in the global genetic network were also typically highly expressed with high connectivity also in protein–protein and chemical-genetic networks.

The team studied the implications of positive versus negative genetic interactions. A prevailing characteristic of gene pairs with negative genetic interactions was that their products operate in a shared biological process or protein complex. In these cases, the negative genetic interaction may arise because the overall complex or process that these genes contribute to suffers only mild impairment following loss of function of single components, but there is synergistic impairment and substantial fitness consequences in the double mutant.

By contrast, functional relationships were more distant between genes displaying positive genetic interactions, which is consistent with broader regulatory or compensatory relationships. For example, diverse detrimental mutations could be compensated by mutations in protein chaperone subunits (to buffer proteotoxic effects) or in cell cycle machinery (which mask the growth defects and/or provide time for the cellular defect to be repaired).

Despite the reliance on a single phenotypic readout of growth rate, this study identifies rich functional information and should serve as a valuable resource for further mining.

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ORIGINAL ARTICLE Costanzo, M. *et al.* A global genetic interaction network maps a wiring diagram of cellular function. *Science* http://dx.doi.org/10.1126/science.aaf1420 (2016)
FURTHER READING Mitra, K. *et al.* Integrative approaches for finding modular structure in biological networks. *Nat. Rev. Genet.* **14**, 719–732 (2013)

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