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EPISTASIS

A network of interactors

If, as some believe, a large portion of the heritability of complex phenotypes resides in synthetic gene–gene interactions, how should we look for these genetic modifiers? Two papers now offer different solutions: one uses a network-guided process and the second is based on patterns of gene co-retention in radiation hybrid (RH) lines.

Studies in model systems show unequivocally that non-additive gene interactions are pervasive in biology. However, searching for modifier loci in humans is hampered by the statistical power required to test the large number (2×10^8) of possible interactions. Lee and colleagues suggest identifying modifiers by using a 'functional gene network' or a map of biological interactions between genes. Provided some knowledge exists about the genetic interactions that underlie a trait, then new modifiers might be detected through their functional connections to these 'seed' genes.

An expanded and improved version of the *Caenorhabditis elegans* functional network (WormNet version 2) includes links between over 15,000 (75%) of worm genes and was generated for this study by incorporating 21 datasets from four eukaryotic species. When it was evaluated on all systematic RNAi screens, WormNet 2 predicted modifiers as well as it could single-gene loss-of-function phenotypes, and performed substantially better than networks based on physical (rather than functional) interactions. An equivalent network in *Saccharomyces cerevisiae* gave similar results, supporting the general use of the approach. WormNet 2 could also predict 31 previously unknown modifiers of three signalling pathways in worm. It should be straightforward to develop a network for humans too, given the extensive functional datasets that already exist, although the requirement for seed modifiers as a starting point might limit the initial application of such a network.

Lin and colleagues followed a different line of thought: they looked for pairs of genes that are preferentially co-retained or preferentially lost across surviving mammalian RH clones. Data were obtained from six publicly available RH panels (from human, mouse, dog and rat) and markers were used to detect over-represented retained or depleted gene pairs across 99% of the genomes. The data, which were combined across the six lines (to improve power), were mapped to the human genome assembly and then used to construct an interaction network at nearly single-gene resolution. The topology of this network — which incorporates more than seven million interactions among 20,000 genes, including >600 unknown ones — suggests that it has reached saturation and some features, such as the high connectivity of essential genes, are consistent with other networks. Most of the interactions involved co-retention of gene pairs and comprised examples of biologically plausible relationships.

Several strategies — computational, experimental, statistical — are being proposed to probe the genome for interactions, and the quick and inexpensive approaches described above highlight the innovative thinking being applied to solve this timely problem.

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ORIGINAL RESEARCH PAPERS Lee, I. *et al.* Predicting genetic modifier loci using functional gene networks. *Genome Res.* 9 June 2010 (doi:10.1101/gr.102749.109) | Lin, A. *et al.* A genome-wide map of human genetic interactions inferred from radiation hybrid genotypes. *Genome Res.* 27 May 2010 (10.1101/gr.104216.109)

FURTHER READING Cordell, H. J. Detecting gene–gene interactions that underlie human diseases. *Nature Rev. Genet.* **10**, 392–404 (2009) | Eichler, E. E. *et al.* Missing heritability and strategies for finding the underlying causes of complex disease. *Nature Rev. Genet.* **11**, 446–450 (2010)

WEBSITE

WormNet version 2: http://www.functionalnet.org/wormnet