COMPLEX TRAITS

Powerful interactions

Interactions between unlinked loci, or epistatic effects, have important roles in shaping human phenotypic variability and disease susceptibility. With the resources and technology for conducting large-scale association studies now imminent, there is a growing need to develop new analytical strategies for detecting and characterizing such interactions on a genome-wide scale.

Detecting interactions between loci requires statistical corrections to account for the extensive multiple testing inherent to multi-locus search strategies, and it is generally assumed that such corrections will weaken the power of the approach. To test this assumption, Jonathan Marchini and colleagues carried out a series of simulation studies to evaluate the performance of analytical strategies that look for interactions between loci. They considered several different two- and three-locus inheritance models using three different gene-detection strategies: a locus-by-locus search, a search over all combinations of loci and a combination two-stage strategy. Surprisingly, they found that, for a large number of epistatic configurations having equal single-locus effects, the interaction-based search strategies were more powerful than the locus-by-locus search strategy, even when a conservative (Bonferroni) correction for multiple testing was used. They concluded that, when analysing genome-wide association data, it might often be advantageous to explore models that explicitly allow for interactions between loci. In particular, they recommend a two-step approach in which single-locus effects are first detected using liberal statistical criteria, followed by a search for all possible interactions among the detected loci under rigorous criteria, corrected for multiple-testing.

The simulation model also reveals that, when interacting loci have different allele frequencies across study populations, the differences in power to detect the marginal effects of each locus can hinder reproducibility. This finding supports recent assertions

GENOME EVOLUTION

Closing in on the hotspots

Recombination ensures genetic diversity. The fact that its distribution across the genome is far from random has been harnessed by human geneticists, most famously in the International HapMap Project. But despite their usefulness, the existence, and above all, the distribution of recombination hotspots has remained a mystery. Two recently published comparisons of fine-scale recombination rates between humans and chimpanzees show that local patterns of recombination evolve very rapidly. The results bring us a step closer to solving the mystery: they hint at the role of epigenetic factors and sequence polymorphisms in determining hotspot location.

Precisely what defines the positions of a recombination hotspot is unknown, but there is evidence for strong sequence specificity, at least in yeast. It has also been suggested that hotspots are short-lived, owing to selection against sites that initiate double-stranded breaks. To take a closer look at the hotspots, Winckler and Myers *et al.* compared fine-scale recombination patterns in chimpanzees and humans. To estimate recombination rates they used recently developed coalescent approaches applied to SNP-polymorphism data to obtain average estimates of recombination rates for both sexes and over many generations.

Initially, their attention focused on two regions: HLA and β-globin. No overlap in hotspot distribution was found here between humans and chimpanzees. Similar results were obtained when the study was extended to three contiguous 500-kb regions, two on chromosome 7 and one on chromosome 4 — although blocks of strong linkage disequilibrium were present in both species, recombination hotspots did not line up.

Ptak *et al.* used a Bayesian approach to reconstruct haplotypes in two regions that consisted of a total of 14 Mb on chromosome 21. They too failed to see any significant conservation of hotspots — location of only 8% was shared between the two species.

Given the evolutionary proximity of humans and chimpanzees, and the degree of sequence conservation between these two species, both sets of the authors conclude that recombination patterns must evolve very rapidly, much faster than the DNA sequence. Since motifs in the primary sequence are unlikely to account for the observed differences in hotspot distribution, both reports favour the involvement of epigenetic factors. As an alternative, Winckler and Myers *et al.* propose an intriguing hypothesis — if the molecules involved in crossover events have a sequence preference, then nucleotide substitutions might have far-reaching consequences for determining hotspot location. The role of SNPs in shaping fine-scale recombination landscape awaits the ultimate proof.

Magdalena Skipper

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that the use of locus-by-locus strategies to analyse interacting loci might be a major contributor to the lack of replication in association studies.

The importance of considering genetic epistasis in the analysis of complex traits is becoming increasingly recognized. By showing here that analytical strategies that explicitly consider interactions between loci are computationally feasible and often yield increased power, Marchini and colleagues offer clear guidance to the community about the design and analysis of future genome-wide association studies.

Kyle Vogan, Associate Editor,
Nature Genetics

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DEVELOPMENTAL BIOLOGY

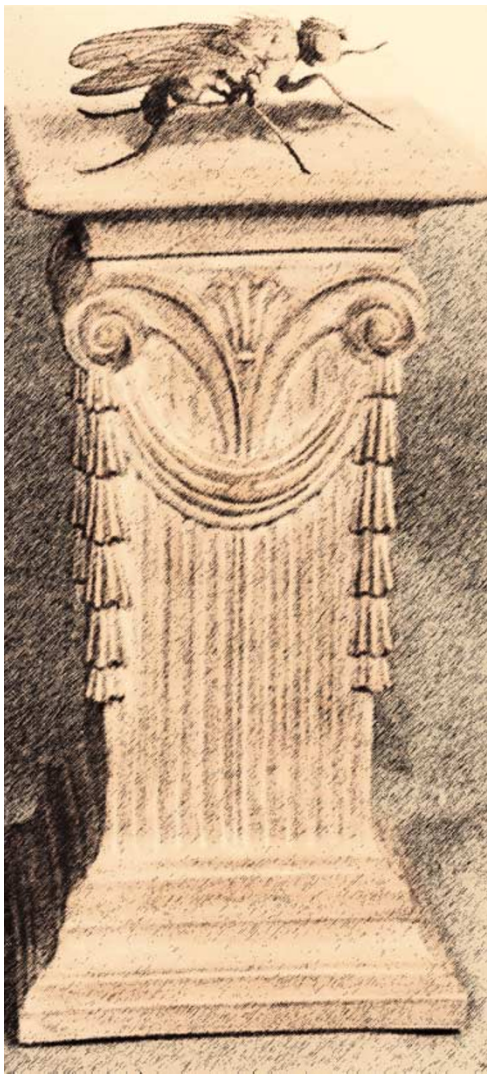
A model model system

In the interdisciplinary spirit that now characterizes much of biology, the hard sciences are increasingly creeping into many aspects of developmental genetics. As two new papers describe, computational methods plus a touch of engineering mean we can model or even build biological systems to refine our understanding of how they work.

Genetic analyses have given us a fairly detailed outline of the signalling hierarchies involved in patterning the nematode vulva and the early development of the fly embryo. However, a more complete view requires tools that can visualize the entire system of cells as well as their dynamic interactions, and that can explore any ramifications the latter might have.

The first study has taken just this approach to studying the vulva of *Caenorhabditis elegans*. This heavily scrutinized part of the anatomy starts out as six multipotent precursor cells (the VPCs), which differentiate to take on one of three fates through the interplay of three signalling events. Modelling what goes on during differentiation involved generating a so-called 'statechart' model for each VPC. This is a visual computational language that describes the behavioural state of a cell at any one time, how it varies depending on the signalling inputs the cell receives and how it interacts with other cells when it is mutated for a signalling component. Although this simulation is still a work in progress, it can analyse VPC specification in some detail — for example, the model highlights the importance of the relative timing of signal reception on the outcome of signalling. The model was built using the bare bones of the vulval network, but adding more recent findings should help to enrich the model and enhance the value of its output.

A second study has applied a creative approach to understanding the elaborate gene network that transforms the maternal morphogen gradient in the fly egg into a neatly patterned embryo. To determine the minimal components required for this process, Mark Isalan and colleagues built an *ex vivo* model of a fly embryo. The syncytium of the early embryo — a pool of nuclei in a common cytoplasm — was recreated by lining a chamber with paramagnetic beads that were coated with DNA encoding different gene constructs, which could then be transcribed, translated and interact with other products as part of a gene network. Tweaking the connectivity of the network yielded different patterns; the system could then be modelled computationally to identify which parameters were compatible with real-life patterns. As for the nematode vulva, this model is simpler than



life, but it suggests several avenues of exploration, such as the realization that diffusion alone cannot bring about the patterns of gene expression seen in real embryos without some sub-localized 'trapping' of the mRNAs or proteins concerned.

Modelling has several advantages over static genetic models; for example, it can easily spot gaps in current knowledge and formulate testable hypotheses. As with all models, it is only as good as the data on which it is based, ensuring that thorough genetic analyses continue to be in high demand.

Tanita Casci

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David Harel's web page: http://www.wisdom.weizmann.ac.il/~dharel
Luis Serrano's laboratory: http://www.embl-heidelberg.de/ExternalInfo/serrano