GENOME WATCH

The battle of the SNPs

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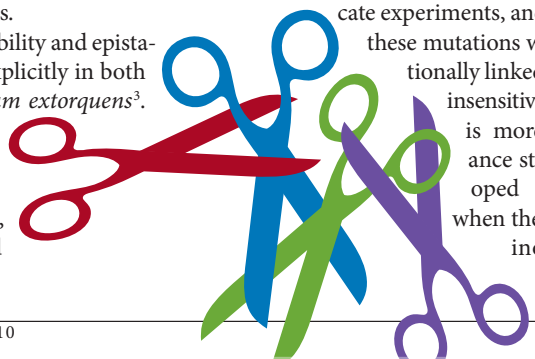
This month's Genome Watch highlights new perspectives on polygenic adaptation and its consequences for fitness in microbial populations.

Accelerating improvements in high-throughput sequencing technologies have allowed researchers to quantify more precisely how known variants (such as single-nucleotide polymorphisms (SNPs)) at different loci can interfere with one another to affect specific traits. This is known as epistasis. By growing microorganisms in controlled laboratory environments, we can now observe the extent to which phenotypes deviate from the expected results using genome-wide comparisons, and examine why such differences arise.

Frozen vials of *Escherichia coli* recently enabled Woods *et al.*[1] to assay changes in fitness over time by replaying the evolution of a range of clones. By measuring the growth rates of the different cloned populations that were merged together in a competitive 'battle of the fittest', they found that the eventual winners were not the leaders throughout the experiment. In fact, the eventual losers climbed an evolutionary peak that led to faster initial gains in fitness but ultimately prevented them from accruing more beneficial polymorphisms later on. This illustrates that the evolvability of a population depends not only on what new variants are generated, but also on the genetic background in which they occur, and stresses the importance of understanding how selection operates on interactions between mutations as well as on the mutations themselves.

The links between evolvability and epistasis have been tested more explicitly in both *E. coli*[2] and *Methylobacterium extorquens*[3]. In each study, the authors identified the major advantageous mutations that had occurred in certain genes, and then progressively mixed different combinations of these beneficial variants together to assess the resulting changes in fitness. In a situation with no genetic constraints between advantageous variants, the effects on fitness should be additive; however, both studies found that the fitness of the combination mutant strains increased with each added mutation but was lower than expected. These results suggest that the general level of negative epistasis is dependent on the pathogen's proximity to its local fitness peak, and that this effect can be gauged from decreasing benefits despite higher expression of the protein conferring the selective advantage. In contrast to these antagonistic interlocus effects, the study on *M. extorquens* also showed that multiple changes within a single gene tend to synergistically promote faster growth than is predicted for each variant alone or in linear combination.

This diminishing-returns model for polygenic epistasis was explored in a more complex scenario that mimicked host cells *in vivo*: the microbial environment was subdivided into compartments with low levels of migration[4]. The authors made a striking finding: increases in *E. coli* population fitness in the presence of the antibiotic ciprofloxacin occurred more quickly in this heterogeneous system than in a standard homogeneous system. Beneficial SNPs could sweep to fixation more quickly in subcompartments with higher drug concentrations, and so resistance to the antibiotic emerged faster overall. Intriguingly, the same set of four resistance mutations was discovered in multiple replicate experiments, and each of these mutations was functionally linked to drug insensitivity. What is more, resistance still developed quickly when the authors inoculated these structured microenvironments with a low number of bacteria, demonstrating that these four antibiotic resistance switches most probably occurred *de novo* as a direct result of the presence of ciprofloxacin. Remarkably, putting the same populations in Petri dishes or shaking liquid culture did not generate any of these four resistance polymorphisms, underscoring how the transient but intricate ecological niches in the compartments represent a different, and perhaps more accurate, model of within-host evolution.



This example indicates that antagonistic epistasis between beneficial variants will slow the emergence of multidrug resistance in pathogens, but that synergistic effects will accelerate this process (see REF. 5 for a review). Analysing the interactions between loci in the context of genomic and fitness changes over time in varied environments will help to outline clinically relevant adaptive landscapes. In addition, the genetic events leading to outbreaks of infectious disease could be further illuminated by studying how recombination, introgression and horizontal gene transfer allow pathogens to enhance their fitness by shifting between evolutionary peaks in dynamic hosts.

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Competing interests statement
The author declares no competing financial interests.