Evidence that adaptation in Drosophila is not limited by mutation at single sites.

Karasov T, Messer PW, Petrov DA
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This is the latest in a series of papers from the Petrov lab arguing for the pre-eminence of selection over other population genetic forces in the recent - and ongoing - evolution of Drosophila melanogaster. In this case the emergence of strong resistance to pesticides introduced by humans in the 1950s is used to challenge the common belief that adaptive evolution is limited by a lack of raw materials - new mutations - in organisms with small long-term effective population sizes.

Karasov et al. began by sequencing the locus responsible for pesticide resistance (the Ace gene) from almost one hundred D. melanogaster strains of diverse origins. They showed that protective variants at amino acid position 161 have arisen independently on three different haplotypes (and continents) and that a highly resistant complex allele (additional changes at positions 265 and 330) is at high frequency among North American D. melanogaster. The rapid response is consistent with pesticide usage constituting a very strong selection pressure; however, the observation of three independent resistance alleles and a compound allele is strikingly at odds with current estimates of the D. melanogaster effective population size. The authors devote the second part of the paper to showing that the multiple haplotypes they observe are hard to explain unless the effective population size is 100 times the currently accepted size of 10^6. Critically, at this level, the product of the effective population size and the mutation rate (theta) is ~1 so all mutations are expected to be present in the population and selection of multiple distinct haplotypes (a 'soft-sweep') ceases to be unlikely. They make three arguments. First, because the protective mutations in the Ace gene are deleterious in the absence of pesticide selection pressure, there is little prospect of pre-existing variation giving rise to their observations.

Second, under a ‘hard-sweep’ model, in which a single protective mutation arises and sweeps to high frequency, the rate of recombination is too low for it to be observed on otherwise diverged haplotypes. Finally, they cite previous work that concludes a soft-sweep of the type they observe is highly unlikely given current effective population size estimates. How is this possible? Is there a major flaw at the heart of the Neo-Darwinian synthesis of evolutionary biology and population genetics? Is the author’s data flawed in some way? Or is there a more subtle problem affecting the analysis? As a resolution to the contradiction, the authors suggest that the effective population size measured by estimates of standing variation (the long-term effective population size) may not reflect the effective population size available to strong natural selection on shorter timescales. Rare but extreme population bottlenecks dominate estimates of effective population size but may have little influence on episodes of strong adaptation that occur between these bottlenecks. The census population size - which can be orders of magnitude larger - may be the more relevant number in such cases. If this is correct then selection may not be mutation limited in D. melanogaster and soft-sweeps may be much more likely than currently appreciated. The authors' conclusions are exciting and have many implications. To highlight just one, the authors argue that more effort should be expended on searching for soft-sweeps in humans and cite the example of lactose persistence. Like insecticide resistance, it represents a case of strong selection that has brought multiple haplotypes to high frequencies. Moreover, one of these is a compound allele. Unlike D. melanogaster, however, neither the effective nor the census population size of humans could have been anywhere close to 10^8 (required to give theta ~1) several thousand years ago, so, unlike Drosophila, human evolution has been limited by mutation. Indeed, the soft-sweep at the lactose persistence locus consists of different alleles that confer the same phenotype. It is noticeable also that lactose persistence is due to a change in expression. As these are likely to offer a much larger mutational target than phenotypes that depend on changes at specific amino acids, this may imply that adaptation in humans is likely to have been concentrated in regulatory rather than coding regions.