LETTER

Recent evidence for pervasive adaptation targeting gene expression attributable to population size change

Addressing the current interest in the role of selection in the evolution of gene regulation, the study by Fraser et al. (1) proposes a test based on coherent effects of *cis* and *trans* expression quantitative trait loci to detect lineage-specific selection on gene expression using genome-wide data from *Saccharomyces cerevisiae*. Based on both this test statistic (a modification of the standard McDonald–Kreitman 2 × 2 contingency table) and population genetic analyses, the authors claim evidence for widespread selective sweeps—concluding that *S. cerevisiae* is evolving primarily through adaptive modification of expression levels.

The authors appropriately note that rejections of the 2 × 2 test may equally be caused by positive selection or relaxed purifying selection. Two features are proposed to uniquely distinguish positive selection: (*i*) reduced levels of variation (i.e., the hitchhiking effect) (2) and (*ii*) because of the same effect, a greater distance between SNPs on average. They reason that, under a model of relaxed purifying selection, levels of variation will increase. Using these criteria, they argue that evolution of gene expression levels in this system mostly results from positive selection.

However, one important limitation of this analysis is a failure to consider the demographic history of these strains (a significant issue for any comparison of sequence heterogeneity in a bottlenecked population, such as the laboratory strains). It is well known that population bottlenecks can replicate patterns of variation associated with selective sweeps (3), both by globally reducing sequence variation and by increasing the variance in local levels of variation. It is this latter characteristic that is particularly hazardous, because localized regions will seem greatly affected (thus replicating the hitchhiking effect). A reduction in effective population size (N_e) also results in a general relaxation in constraint, because the selective effect of a mutation is determined by the product of N_e and the selection coefficient, s.

By fitting a population bottleneck to the observed levels and variance of diversity between the wild and laboratory strains, it is possible to evaluate whether these observations are consistent with a purely neutral model. Estimating a 99.3% reduction in population size associated with the founding of the laboratory strains, Fig. 1 plots a random simulated realization of diversity between strains. As shown, the empirically observed local reductions in sequence variation occur under this model. Furthermore, extrapolating the estimated values to N_e (taken as the harmonic mean of population size), we estimate N_e_lab/N_e_wild = 0.59. Thus, polymorphisms evolving under strong or weak purifying selection in the wild population are expected to become weakly selected or neutral, respectively, in the laboratory strains.

These results show the ability of a neutral model to explain both the observation of significant 2 × 2 contingency tests and the subsequent follow-up analyses centered on a reduction in variation (consistent with previous observations of limited adaptive evolution in yeast) (4). This neutral bottleneck further accounts for the authors' observation of greatly increased selection in the laboratory strains relative to the wild, which they indeed note as perplexing because it is counter to $N_e s$-based expectations.

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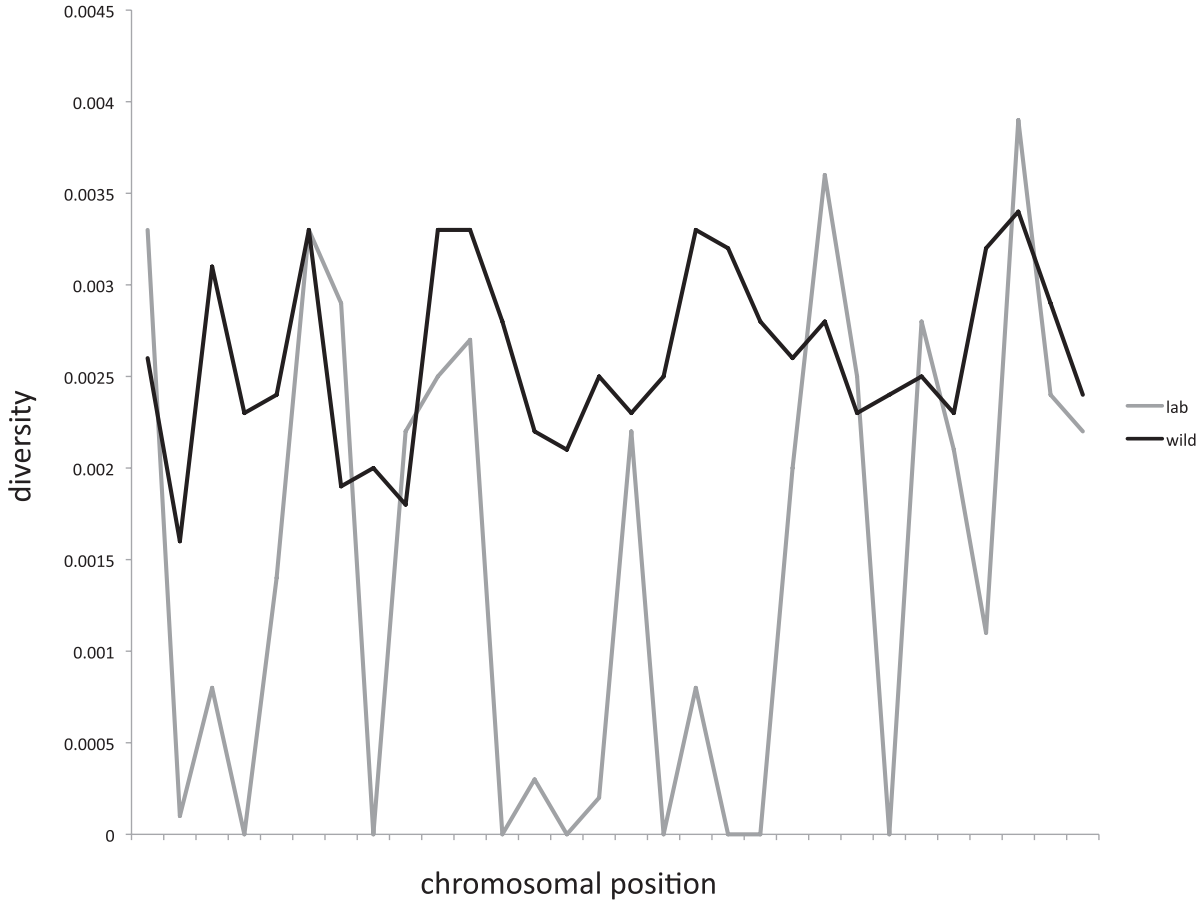

Fig. 1. Simulated plot of variation under a neutral model [using the program ms (5)]. The laboratory strain has experienced the bottleneck estimated from the data (empirically observed mean = 0.0015; variance = 0.0013), whereas the wild strain is simulated at equilibrium (empirically observed mean = 0.0026; variance = 0.0005).