The Joint Distribution of Fitness Effects for Beneficial Mutations. G. Sherlock[1], L. Herissant[1], D. Yuan[2], P. Humphrey[3], M. Johnson[3], A. Agarwala[4], D. S. Fisher[4], M. Desai[3], D. A. Petrov[2]. [1]Department of Genetics, Stanford University, Stanford, California 94305-5120, USA., [2]Department of Biology, Stanford University, Stanford, California 94305, USA, [3]Departments of Organismic and Evolutionary Biology and of Physics, and FAS Center for Systems Biology, Harvard University, Cambridge, Massachusetts 02138, USA., [4]Department of Applied Physics, Stanford University, Stanford, California 94305

When microbes are propagated in a simple, unstructured environment over hundreds of generations, mutations that provide a fitness benefit under that condition, if they escape drift, are selected and increase in frequency. However, such adaptive mutations are unlikely to be beneficial under all experimental conditions (environments), or indeed might not be beneficial under many other conditions at all. A specific example is when a mutation is beneficial in one condition, but deleterious in other conditions, a phenomenon known as Antagonistic Pleiotropy (AP). AP is thought to lead to evolutionary trade-offs and the persistence of deleterious alleles. However the prevalence of AP remains largely unexplored, and it is unknown which genes or pathways are more likely to be involved in AP.

To systematically answer these questions, we are using an experimental system that we developed to track and measure the fitness of up to ~500,000 lineages within an evolving yeast population via DNA barcodes [1]. This system also allows us to remeasure the fitness of selected evolved clones across multiple environments with high precision [2]. For this work, we have extended our lineage tracking system to include a second, condition specific barcode, and then evolved barcoded haploid and diploid yeast populations under 12 different environments. By low coverage barcode sequencing, we are able to determine a timepoint from which to isolate sufficient numbers of adaptive clones for fitness remeasurement. From these data, we observed that haploid populations tend to evolve faster than diploids, and hypothesize that this is because recessive mutations will have a fitness effect in haploids, but not diploids. From an appropriate timepoint, we have isolated hundreds of clones from each of the evolving haploid populations, and are now remeasuring their fitness (in a pooled fashion, due to the presence of the condition specific barcode). Preliminary data allow us to make two general observations. First, beneficial mutations selected in one environment may be beneficial, neutral or deleterious in other environments. Second, even when mutations selected in one environment are beneficial in a second, they are not as beneficial as the mutations that are specifically selected in that second environment.

Finally, we have begun whole genome sequencing of beneficial clones, with the goal of sequencing >1,000 clones from across all of the evolutionary environments. For the first two conditions from which we have sequenced clones, which are evolution in the presence of either clotrimazole or fluconazole, despite the fact that these are both azole based antifungal drugs, we find that their mutational spectra are quite different.

These experiments will result in the largest set of fitness measurements for adaptive mutations ever collected across multiple environments. It will allow us to determine, for example, the extent of AP among new beneficial mutations and any correlations between the magnitudes of effects. The results will provide the first insight of how mutation-driven processes can confer selective advantage or why deleterious alleles can be retained by evolution.

References:

[1] Levy S. F., Blundell J. R. *et al.*, (2015) *Nature*, *519*, 181-186. [2] Venkataram S., Dunn B. *et al.*, (2016) *Cell*, *167*, 1585-1596