

Impact of negative selection on the genetic architecture of diseases and complex traits.

Abstract: It is widely known that negative selection against genetic variants that reduce fitness causes them to be enriched for lower-frequency variants, so that lower-frequency variants have larger causal effects on diseases and complex traits. Here, we explore two other ways in which negative selection impacts disease and trait architectures. First, we show that (conditional on minor allele frequency) variants with low levels of linkage disequilibrium have larger causal effects. We show that much of this signal can be explained by the fact that (conditional on minor allele frequency) more recent variants have larger causal effects, since negative selection has had less time to remove them; for example, the youngest 20% of common variants explain 4x more heritability than the oldest 20% of common variants. Second, we show that functional annotations strongly impacted by negative selection have larger enrichment for low-frequency variant heritability compared to their enrichment for common variant heritability, both empirically and in forward simulations. Cell-type-specific regulatory annotations that are enriched for common variant heritability tend to be similarly enriched for low-frequency variant heritability for most annotations and traits, but more enriched for brain-related annotations and traits.

For example, H3K4me3 marks in brain DPFC explain $57 \pm 12\%$ of low-frequency variant heritability vs. $12 \pm 2\%$ of common variant heritability for neuroticism, implicating the action of negative selection on low-frequency variants affecting gene regulation in the brain.

Bio: Dr. Price is a Professor in the departments of Epidemiology and Biostatistics at the Harvard T.H. Chan School of Public Health, and an Associate Member at the Broad Institute of MIT and Harvard. His research focuses on the development of statistical methods for uncovering the genetic basis of human disease, and on the population genetics underlying these methods. Areas of interest include functional components of disease heritability, common vs. rare variant architectures of disease, and disease mapping in structured populations.