Evidence of widespread selection on standing variation in Europe at height-associated SNPs

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The extent to which different types of selection have influenced patterns of variation in the human genome remains largely unknown. One type of selection, recent positive selection acting on newly arising genetic variants, produces a strong genetic signature -- a long haplotype of unexpectedly high frequency -- which has been well studied and documented both at candidate loci and in genome-wide studies. However, recent work has suggested that strong positive selection on new mutations may not be widespread in recent human evolution. Because many human traits are highly polygenic and at least partly influenced by common, ancient genetic variation, an alternative model has been hypothesized to be important for genetic adaptation in humans, namely, weak polygenic selection acting on many pre-existing (standing) genetic variants. Here we demonstrate the first empirical example of widespread weak selection on standing variation in humans by studying height-associated variants in Northern (NEur) and Southern (SEur) Europeans. We show that the frequencies of alleles that have been associated at genome-wide significance with increased height are systematically elevated in NEur compared with SEur ($p<4.3\times10^{-4}$). This pattern persists across many additional variants throughout the genome, and is not due to confounding by ancestry or other potential ascertainment biases. The observed frequency difference is also much more consistent with evolutionary models incorporating both genetic drift and widespread weak selection (selection coefficients ~10^{-3}-10^{-5} per allele) than with drift alone (likelihood ratio $p<10^{-15}$). Our results demonstrate the presence of widespread selection in humans on standing variation for height, a classic polygenic trait. Moreover, our approach can be used to search for other examples of human polygenic adaptation, including traits or diseases associated with climate or other environmental variables that vary across otherwise closely related populations, as more trait-associated variants are identified through extensive resequencing studies.