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Advantageous diversity maintained by balancing selection in humans

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Most human polymorphisms are neutral or slightly deleterious, but some genetic variation is advantageous and maintained in populations by balancing selection. Considered a rarity and overlooked for years, balanced polymorphisms have recently received renewed attention with several lines of evidence showing their relevance in human evolution. From theoretical work on its role in adaptation to empirical studies that identify its targets, recent developments have showed that balancing selection is more prevalent than previously thought. Here we review these developments and discuss their implications in our understanding of the influence of balancing selection in human evolution. We also review existing evidence on the biological functions that benefit most from advantageous diversity, and the functional consequences of these variants. Overall, we argue that balancing selection must be considered an important selective force in human evolution.

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Introduction

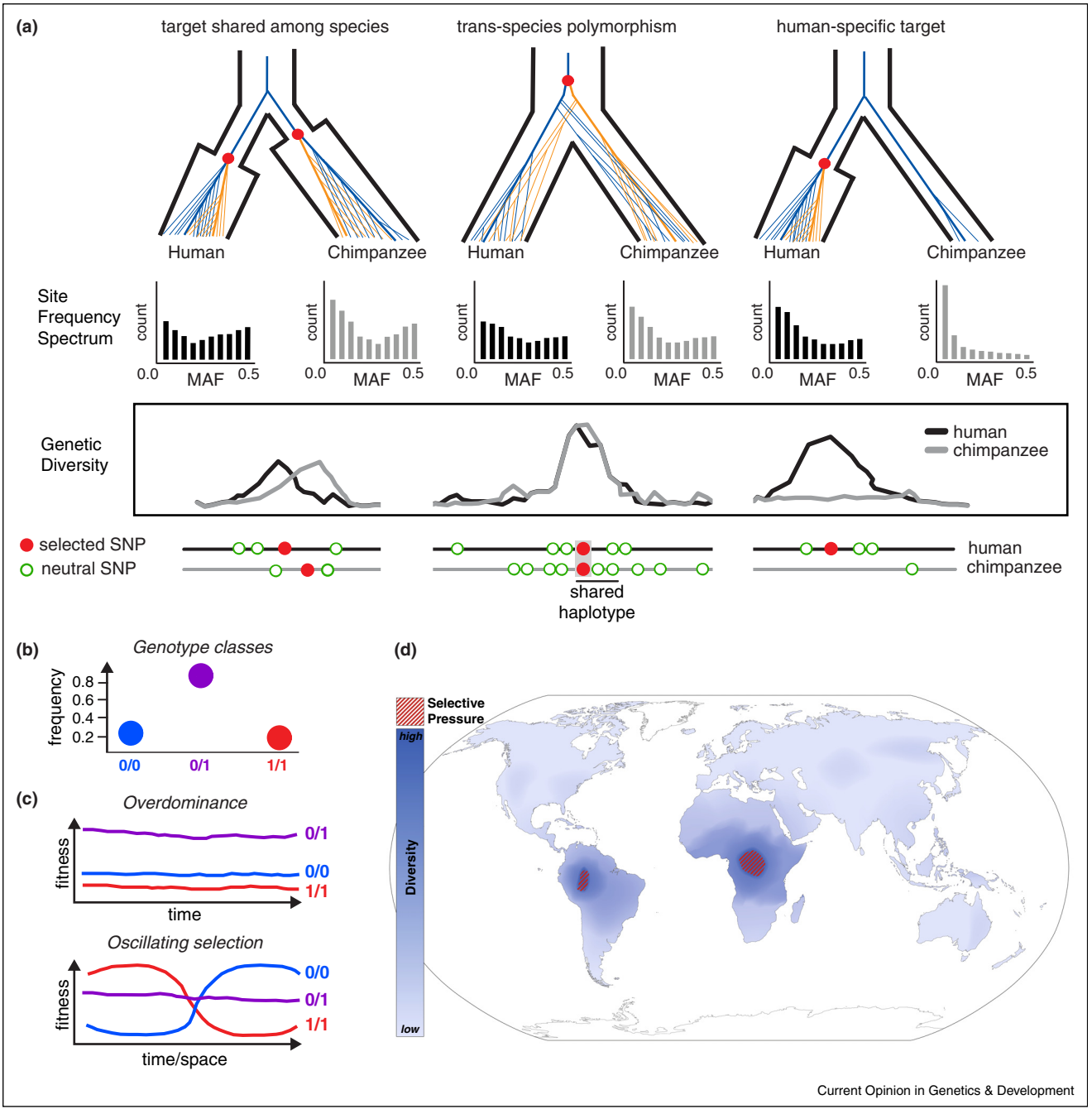
Humans are genetically fairly homogeneous, with low levels of genetic variation that is found mostly within (rather than between) populations. The vast majority of this variation is neutral or slightly deleterious, but there are also advantageous polymorphisms maintained by natural selection. A classical example is a polymorphism in the β-globin gene. Homozygote individuals for this variant are either susceptible to malaria (HbA/HbA genotype) or suffer from sickle cell anemia (HbS/HbS), while heterozygotes have a higher chance of surviving malaria [1]. Hence, heterozygotes have higher fitness in regions where malaria is endemic, and both alleles are maintained in the population. Such heterozygote advantage (also known as overdominance or heterosis) can maintain stable polymorphisms, as can other mechanisms such as frequency-dependent selection, certain changes in selection in time or space in well-defined populations, or pleiotropy [2–4,5•,6,7], all of which can be considered classical types of balancing selection.

Identifying balancing selection

Balanced polymorphisms will be maintained in a population as long as selection can overcome the effects of drift and prevent allele fixation. Selection that is old will maintain advantageous polymorphism and result in an older time to the most recent common ancestor (TMRCA) than expected under neutrality [8••]. This results in the accumulation of neutral, old linked variation, segregating at a frequency close to the frequency equilibrium (i.e. the frequency that maximizes fitness in the population) and an excess of polymorphic over divergent sites [9]. These footprints in the patterns of linked variation exist (albeit with some differences) under all types of long-standing balancing selection, and although the signatures are narrow because of the long-term effects of recombination [9,10], they leave recognizable local patterns that can be used to identify targets of balancing selection (the loci under balancing selection) (see Figure 1a and section *Balancing selection in humans* below). Importantly, the excess of variation differentiates targets of long-term balancing selection from loci under recent selection or an incomplete selective sweep. When selection is shared across populations it will also result in unusually low population differentiation, a pattern classically identified via unexpectedly low allele frequency differences (e.g. F_{ST} values [11]).

Balancing selection is per se a stable form of natural selection that can persist for millions of years. When selection spans speciation events and continues to act in the new species, old balanced polymorphisms can continue to segregate until present-day populations of the different species. Such trans-species polymorphisms are unexpected under neutrality for species that diverged long ago and are a hallmark of long-term balancing selection [12–15]. We refer readers to Figure 1a and manuscripts below for signatures of trans-species polymorphisms, but we note that it involves haplotypes clustering by allelic type rather than by species, extremely high diversity, and in some cases the presence of more

Figure 1



Strategies to identify balancing selection. **(a)** Using patterns of linked variation, including high genetic diversity and shifts in the folded site frequency spectrum (MAF is minor allele frequency). **(b)** Observing departures of Hardy-Weinberg Equilibrium (stable excess of heterozygotes). **(c)** Measuring fitness differences among genotype classes (e.g. overdominance and oscillating selection). **(d)** Detecting an unexpected correlation between genetic diversity and a given selective pressure.

than one linked variant as trans-species short haplotypes [13,14,16••,17,18•,19] (Figure 1a).

Observing the direct effects of balancing selection is the most convincing evidence of its influence. For example, in the absence of genotype errors and population substructure, a significant excess of heterozygotes (also known as Hardy-Weinberg disequilibrium) provides preliminary evidence that heterozygotes may have increased survival, a signature of overdominance (Figure 1b). Even