Supporting Text

Estimates of Selection and Dominance Parameters. We investigated the influence of dominance relationships (h) on estimates of selection intensity based on the ratio (r) of U-to-P polymorphic derived mutations (γ_r) and on the difference in frequency (Δf) between P and U mutations ($\gamma_{\Delta f}$). Our results (see Fig. 6) are based on the analytical predictions under the infinitely many sites model and mutation-selection-drift (MSD) equilibrium (1-4). We observe that variation in h, including complete dominance ($h \approx 1$) or recessivity ($h \approx 0$), has a minor effect on r and hence on estimates of γ_r for moderately large sample sizes. [The influence of variable h on r increases with sample size, and it is negligible when the sample size is small (data not shown).] In contrast, different dominance relations strongly influence Δf, biasing our estimates of $\gamma_{\Delta f}$ if genic selection is assumed; the more recessive an advantageous mutation (i.e., P mutation), the weaker the effect of γ on Δf. That is, the common assumption of genic selection ($h \approx 0.5$) will overestimate (or underestimate) the true $\gamma_{\Delta f}$ if P mutations are partially dominant (or recessive).

Frequency of Favored Codons, Mutational Biases, and Dominance. Assuming the infinitely many sites model and MSD equilibrium, the fraction of favored codons in a sequence (P) can be estimated as a function of γ and mutations rates, where u_1 and u_2 are mutation rates at favored and nonfavored sites that will generate nonfavored and favored sites, respectively,

$$P = \frac{e^{2\gamma}}{w + e^{2\gamma}},$$

with $w = u_1/u_2$ (1, 5, 6). w is an index of the mutational bias, and $w > 1$ indicates mutational bias toward AT content. Note that this formula to estimate P is valid for any

dominance parameter (unpublished data), and therefore the study of the change in P (ΔP) due to variation in w is also valid for any dominance parameter.

Nonstationarity Caused by Changes in BGC and/or *w*. To study the possible causes of nonstationarity at synonymous sites in the human lineage, we investigated two neutral mechanisms expected to increase the number of fixed AT and U mutations, relative to GC and P mutations, and their effects across isochores. The first mechanism is associated with a genome-wide increase in the mutation rate toward AT (w); the second is a consequence of a genome-wide reduction in the effects of bias mismatch repair during gene-conversion events (BGC) (7), hence causing a relative increase in AT content. We investigated the analytical predictions under the infinitely many sites model and MSD equilibrium (2, 4-6) (Fig. 8). We observe that an increase in w will generate a pattern that is close to that observed, with a maximum relative reduction in GC content in genes located in isochores with intermediate GC content. In contrast, we observe that the neutral scenario caused by a reduction in the effects of BGC generates a pattern with stronger effects in genes located in GC-rich isochores.

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