Supporting Methods

Fixation Probabilities for Autosomal and X-Linked Mutations. Most of the results were obtained in refs. 1 and 2. We simplify them below and explain how we use them in our calculations.

Throughout this paper, we assume mating is random. We also assume selection acts constantly and equally on the two sexes, with dosage compensation. In other words, the fitnesses of female genotypes XX:Xx:xx are 1:1+hs:1+s, and the fitnesses of male genotypes XY:xY are 1:1+s, where x is the new mutation.

Let us assume an ideal population with size N (N is also the effective population size N_e), and the frequency of a new mutation q. Its fixation probability is given by

$$u = \frac{\int_0^q G(x)dx}{\int_0^1 G(x)dx},$$

where $G(x) = e^{-\int \frac{2M_{\delta x}}{V_{\delta x}}dx}$; $M_{\delta x}$ and $V_{\delta x}$ stand for the mean and variance of the change in the mutant frequency per generation (3). We shall use ' to designate values for X-linked genes.

For an autosomal mutation, ref. 3 shows

$$M_{\delta x} = sx(1-x)[h+(1-2h)x],$$

$$V_{\delta x} = \frac{x(1-x)}{2N} \qquad\qquad\qquad \textbf{[1]}.$$

For an X-linked mutation, ref. 1 shows

$$M_{\delta x} = \frac{1}{3}sx(1-x)[2h+2(1-2h)x+1],$$

$$V_{\delta x} = \frac{x(1-x)}{2N'} \qquad\qquad\qquad \textbf{[2]},$$

where $N' = \frac{3}{4}N$.

The fixation probability of a new mutation under selection, relative to that of a neutral mutation, is

$R = u/q$ for autosomal genes and

$R' = u'/q'$ for X-linked genes. [3]

Here we assume $q = \dfrac{1}{2N}$ and $q' = \dfrac{1}{2N'}$.

In many sexually reproducing species, the effective numbers of breeding females (N_f) and males (N_m) are not equal. Hence, N_e is no longer equal to N and has to be reformulated for Eqs. **1** and **2** (see ref. 4 for various conditions). In general, males tend to have a larger variance in reproductive success. In both human and chimpanzee, since their separation, the strength of sexual selection is considered modest relative to other mammals on account of the low degree of sexual dimorphism in these two species (5).

If only a fraction (m) of males contribute to breeding, then

$$N_m = \frac{m}{2}N,$$

$$N_f = \frac{1}{2}N.$$

The effective population size for autosomal genes is $N_e = \dfrac{2m}{1+m}N,$ and, for X-linked genes, is $N_e' = \dfrac{9m}{4+8m}N$ (6). These N_e and N_e' formulae are used in Eqs. **1** and **2**. In the human lineage, m has been suggested to be between 1/3 and 1 (5).

Point Estimates of the Proportion of Synonymous Substitutions Under Negative Selection. Suppose a proportion of synonymous changes, p, are deleterious with the selection intensity s, and the rest, $1-p$, are advantageous to the same degree. The fixation probabilities of synonymous substitution relative to neutrality for autosomal (K) and X-linked (K') genes are

$$K = p \cdot R^- + (1-p) \cdot R^+,$$

$$K' = p \cdot R'^- + (1-p) \cdot R'^+,$$

where R^- and R'^- are, respectively, the fixation probabilities (u and u') of new mutations under purifying selection relative to those of neutral mutations for autosome and X chromosome, and R^+ and R'^+ are the fixation probabilities of new mutations under positive selection relative to those of neutral mutations for autosome and X chromosome. $R^-, R'^-, R^+,$ and R'^+ are given in Eq. **3**.

If we assume intergenic regions (i) to evolve neutrally, then $\hat{K} = 0.791$ (K_s/K_i for autosomal genes) and $\hat{K}' = 0.706$ (K_s/K_i for X-linked genes). For each h and m combination, we evaluated K (or K') with a series of ps (ranging between 0 and 1 with a 0.01 increment) and $2N_es$ (ranging from -6 to 0 with a 0.1 increment), which determine the fixation probabilities. In Table 6, we show the values of p and $2N_es$ that have the best fits between the theoretical K (K') and the observed values by the following least-square formula: $\text{Min}((\hat{K} - K)^2/K + (\hat{K}'-K')^2/K')$.

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