SUPPLEMENTARY INFORMATION

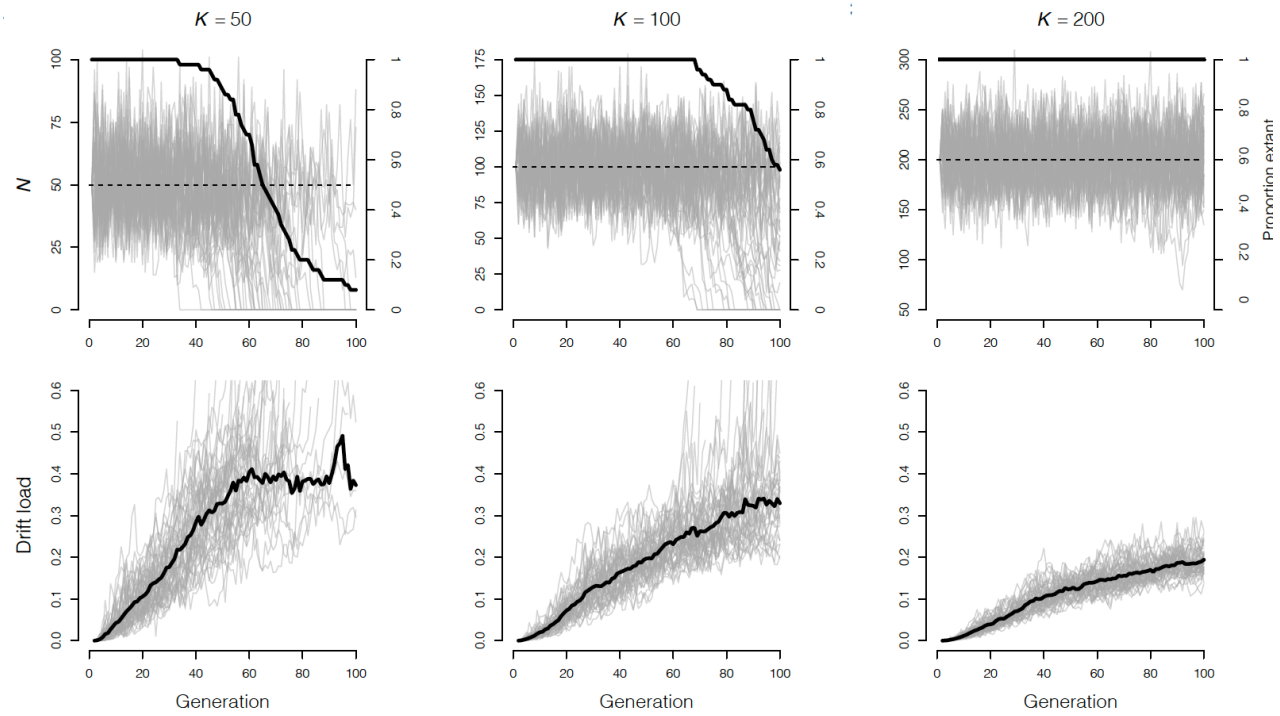

Figure S1. Mutational meltdown via *de novo* mutation in isolated populations. Panels in the top row show population size N (gray lines, left vertical axis), and the proportion of extant populations (thick black line, right vertical axis) for 50 replicate simulations of populations with carrying capacities (K) of 50 (**A**), 100 (**B**), and 200 (**C**). The bottom row shows the drift load for each simulation replicate (gray lines), and the mean across all non-extinct populations (thick black line). These simulations with hard selection have a ratio of effective population size (N_e) to N of approximately 0.25 on average (Figure S5).

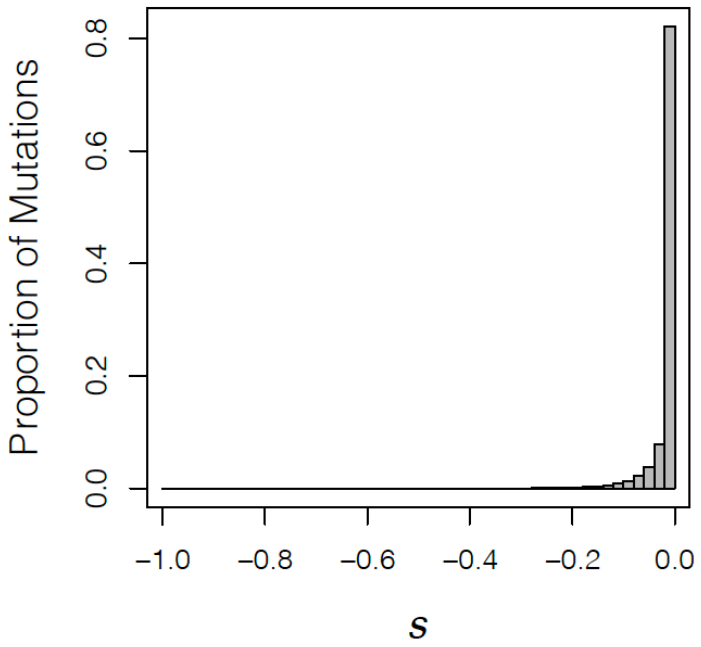

Figure S2. Gamma distribution (shape parameter = 0.186 and scale parameter = 0.071) of fitness effects (*s*) for deleterious mutation assumed in Teixeira and Huber (2021), Robinson et al. 2018, and Kyriazis et al. (2020). Highly deleterious mutations are effectively excluded here (compare to Figure S4 and the results reviewed in Eyre-Walker & Keightley (1)).

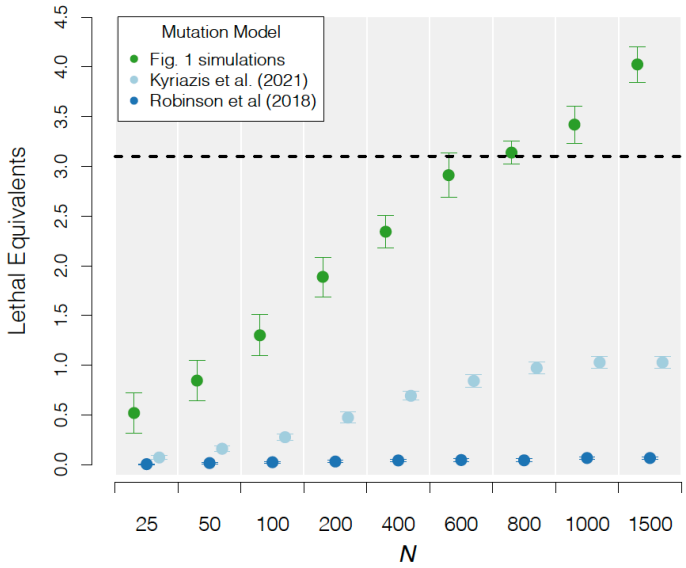

Figure S3. Number of lethal equivalents at approximate mutation-drift-selection equilibrium under the mutation models of Kyriazis et al. (2), Robinson et al. (3), and the simulation model in Figure 1 for constant population sizes ranging from N_e = 25 to N_e = 1,500. The error bars represent the standard deviation across 10 simulation replicates. The dashed line represents the median number of lethal equivalents for juvenile survival for captive mammals from Ralls et al. (4). Note that O'grady et al. (5) estimated an average of 12 lethal equivalents across all fitness components in wild mammals.

Simulations illustrating the relationship between genetic variation and fitness

We use individual-based simulations implemented in R (6-9) to illustrate the relationships among genetic variation, population size, additive genetic variance (V_a), inbreeding load, drift load, and population viability. These are intended to demonstrate patterns that arise directly from population genetics theory under empirically supported combinations of the key parameters. The simulated organism is a self-incompatible hermaphrodite, and has non-overlapping generations, and mean fecundity of 4 (6) when selection was hard (population size is temporally variable), and 2 when selection was soft (population size is temporally constant). Details on the implementation of hard versus soft selection are provided below. Partially recessive deleterious mutations, and mutations that affect the quantitative trait affect fitness by viability selection before breeding when population size is temporally variable (selection is hard), and during the reproduction phase when

population size is constant (selection is soft). The simulations in Figures 1 & 2 in the main text include both partially recessive mutations (as described below), and mutations that affect a quantitative trait (also described below). The simulations shown in Figures 3 (main text), S1, and S3 include partially recessive deleterious mutations, but do not incorporate selection on a quantitative trait.

Simulations with temporally variable population size (Figures 3 & S1) assume a ceiling model of density dependent fitness. Here, when population size is > carrying capacity (K), mean fitness is penalized so that the expected number of offspring forming the next generation is K.

Mutations affecting a quantitative trait under stabilizing selection

Our model for the inheritance of a quantitative trait is from Kardos & Luikart (6). The quantitative trait is assumed to have an optimal phenotype value of $\theta = 0$ (in arbitrary units), a per diploid genome per generation mutation rate of $U_q = 0.147$, with phenotypic effects (a) drawn from a uniform distribution ranging from -0.5 to 0.5, an environmental variance of $V_e = 4$. We assume a Gaussian fitness function:

$$W_{q,i}(z) = W_{\max} e^{-\frac{(z_i-\theta)^2}{2c^2}}, \qquad (1)$$

where $W_{q,i}(z)$ is the expected fitness of individual i with quantitative trait value z_i, c is the standard deviation of the fitness function [set to $c = 6$ as in (6)], z is the individual's phenotype value, and $W_{\max}$ is the expected fitness of an individual with phenotype of $z = \theta$ and no partially recessive deleterious mutations (set to $W_{\max} = 2.5$). $W_{\max}$ is equivalent to the intrinsic population growth rate for a perfectly adapted population with population size very near zero. Smaller values of $W_{\max}$ (e.g., $W_{\max} = 1.5$) resulted in nearly all large populations going to extinction before reaching mutation-drift-equilibrium for lethal equivalents when selection was hard (see below).

Deleterious mutations affecting fitness

Deleterious mutations act directly on individual fitness. We assume a deleterious mutation rate per diploid genome of $U = 1.2$, as observed in *Drosophila* (10), which is substantially lower than in hominids ($U = 1.6$) (11). The location of a mutation is assigned randomly across 38 chromosomes, the number of autosomes in *Canids* (12), each with a 50 cM genetic length. We assume a gamma

distribution of mutation fitness effects (s, the expected reduction in fitness for derived allele homozygotes relative to wild type homozygotes), with shape parameter = 0.5 and scale parameter = 0.1, augmented so that 5% of deleterious mutations are lethal (Figure S4). This distribution mimics the distribution of fitness effects observed in mutation accumulation experiments (1), and is consistent with known contribution of both lethal and small-effect, partially recessive mutations in model organisms, humans, and non-model organisms, e.g., (13-15). We assume an exponential model of the relationship between dominance (h) and s as $h = 0.5e^{-13s}$, which closely mimics experimental results in model organisms (16, 17), where mutations with s very near 0 are generally nearly additive ($h \approx 0.5$), and mutations with s near -1 (lethals) are essentially completely recessive ($h \approx 0$, Figure S4). Using the higher deleterious mutation rate of hominids would result in an even larger gap between the resulting fitness effects of inbreeding here compared to Teixeira & Huber (18), Robinson et al. (3), and Kyriazis et al. (2) (Figure S3).

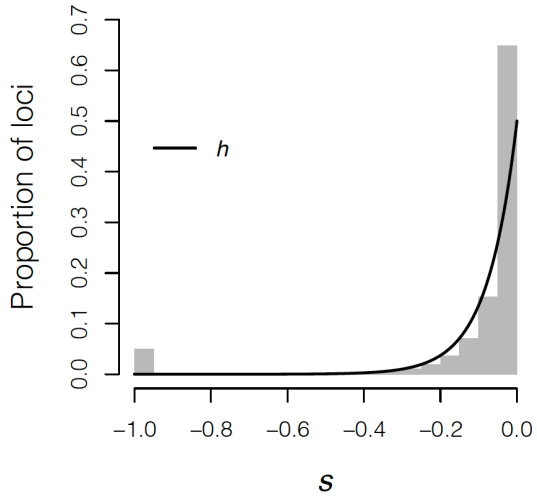

Figure S4. The distribution of selection coefficients (s) for deleterious mutations in our simulations. The black line shows the dominance coefficient h as a function of s.

The fitness reduction arising from partially recessive deleterious mutations for individual i is calculated as

$$\Delta W_i = \sum_{j=1}^{n} \eta_{i,j} \begin{cases} h_j s_j & \text{if } \eta_{i,j}=1 \\ s_j & \text{if } \eta_{i,j}=0 \text{ or } 2 \end{cases}, \qquad (2)$$

where $\eta_{i,j}$ is the count of the derived deleterious allele at the jth of the n loci where there has been a deleterious mutation in individual i. h_j and s_j are the dominance and selection coefficients, respectively, at locus j. Subtracting ΔW_i from $W_{q,i}(z)$ (eq. 1) yields the expected fitness of individual i given the fitness effects of the quantitative trait and partially recessive deleterious mutations.

Hard versus soft selection

Some of our simulations force population size to be constant (Figures 1, 2, S3) to simplify our analyses of the effects of population size on the parameters of interest. Constant population size implies that selection on the phenotype and arising from deleterious mutations was soft. Here, the mean fecundity is by definition 2, such that the population growth rate is exactly $\lambda = 1$, and the expected fitness of an individual with a particular genotype depends on the genotypes of others in the population (19). Selection in these cases is implemented during the reproduction phase.

Our other simulations allowed population size to fluctuate through time (Figures 3 and S1) to illustrate genetic effects on population viability. When population size is allowed to fluctuate through time, selection is hard, where an individual's fitness depends only on its genotype, and population fitness (population growth rate) depends on the collection of genotypes of all the individuals in the population (19). Here, selection is imposed via selection on juvenile survival before the breeding phase.

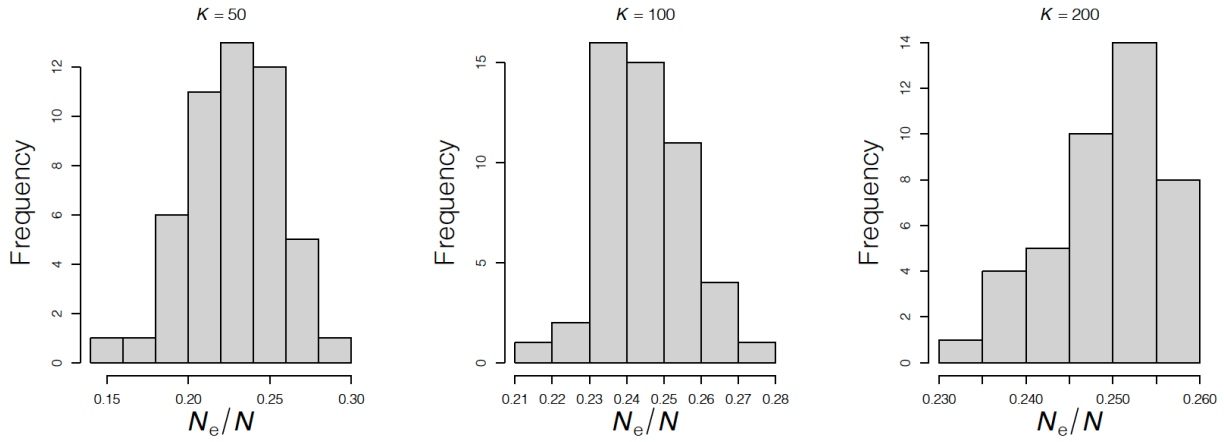

Figure S5. Distributions of the ratio of effective population size (N_e) to census population size (N) in simulations from Figure S1. N_e was calculated as $N_e = (1/\overline{\Delta F})/2$, where $\overline{\Delta F}$ is the mean per generation change in the pedigree inbreeding coefficient in the population over the first 50 generations of the simulation.

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