Influence of Dominance, Leptokurtosis and Pleiotropy of Deleterious Mutations on Quantitative Genetic Variation at Mutation-Selection Balance

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ABSTRACT

In models of maintenance of genetic variance (V_G) it has often been assumed that mutant alleles act additively. However, experimental data show that the dominance coefficient varies among mutant alleles and those of large effect tend to be recessive. On the basis of empirical knowledge of mutations, a joint-effect model of pleiotropic and real stabilizing selection that includes dominance is constructed and analyzed. It is shown that dominance can dramatically alter the prediction of equilibrium V_G. Analysis indicates that for the situations where mutations are more recessive for fitness than for a quantitative trait, as supported by the available data, the joint-effect model predicts a significantly higher V_G than does an additive model. Importantly, for what seem to be realistic distributions of mutational effects (*i.e.*, many mutants may not affect the quantitative trait substantially but are likely to affect fitness), the observed high levels of genetic variation in the quantitative trait under strong apparent stabilizing selection can be generated. This investigation supports the hypothesis that most V_G comes from the alleles nearly neutral for fitness in heterozygotes while apparent stabilizing selection is contributed mainly by the alleles of large effect on the quantitative trait. Thus considerations of dominance coefficients of mutations lend further support to our previous conclusion that mutation-selection balance is a plausible mechanism of the maintenance of the genetic variance in natural populations.

GENETIC variation in quantitative traits is a ubiquitous phenomenon. As the only ultimate source of genetic variation, mutations change their carriers' values of both the metric trait and fitness. That is, mutations input fresh polygenic variance into the population and at the same time put the population under selection by decreasing their carriers' fitness to a varying extent. These conflicting effects of mutations appear to suggest small genetic variation. However, high levels of genetic variance (V_G; *i.e.*, a heritability in the range 25–50%) are observed typically in natural populations for quantitative traits, and it has usually been assumed that traits are under strong stabilizing selection, with apparent strength ($V_{s,t}$) $\sim 20 V_e$ (Turelli 1984; Endler 1986; Falconer and Mackay 1996). [However, Kingsolver *et al.* (2001) recently concluded that stabilizing selection might be substantially weaker than has been assumed.] Here $V_{s,t}$ is expressed as the "variance" parameter of the pseudo-Gaussian fitness function, where high $V_{s,t}$ implies weak selection. Although attracting much theoretical attention, the mechanism of the maintenance of the genetic variance in quantitative traits under stabilizing selection that should rapidly deplete that variance in natural populations still remains an open problem (see Falconer and Mackay 1996, Chap. 20; Bürger 2000; Barton and Keightley 2002). In classical models it is assumed that natural selection acts either directly on the metric trait (*i.e.*, *real* stabilizing selection; Kimura 1965; Turelli 1984; Bürger 2000) or on the mutant genes that affect both the trait and fitness (*i.e.*, *pure* pleiotropic selection; Barton 1990; Keightley and Hill 1990; Kondrashov and Turelli 1992). Assuming that the metric trait is not neutral and undergoes real stabilizing selection, nevertheless, a model in which pleiotropic and real stabilizing selections are combined can induce significant stabilizing selection as well as substantial genetic variance (Zhang and Hill 2002). However, it still has difficulty in accounting for the observed levels of V_G and $V_{s,t}$ for what appear to be realistic mutational effects, *e.g.*, many fewer genes substantially affecting the metric trait than fitness. In that model, as in most mutation-selection balance models of genetic variation, mutants were assumed to be additive.

Properties of mutations such as the distribution of their effects and degree of dominance are fundamental to many phenomena, such as the evolution of sex (Chasnov 2000; Keightley and Eyre-Walker 2000; Agrawal and Chasnov 2001), the long-term response to artificial selection (Robertson 1960; Hill 1982a), the mutational load (Charlesworth and Charlesworth 1999; Wang and Hill 1999), and the maintenance of genetic variation (Keightley and Hill 1990; Caballero and Keightley 1994). Although a great deal of

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research effort has been put into its study (Simmons and Crow 1977; García-Dorado *et al.* 1999; Keightley and Eyre-Walker 1999; Lynch *et al.* 1999), knowledge of properties of mutations is still very limited. Nonetheless, it is widely believed that the distributions of homozygous effects of mutations are leptokurtic and highly deleterious mutations tend to be nearly recessive (Simmons and Crow 1977; Charlesworth 1979; Mackay *et al.* 1992; Caballero and Keightley 1994; García-Dorado *et al.* 1999, 2003; Lynch *et al.* 1999). It is also reasonable to assume that the distribution of homozygous effects of mutations on fitness should be less leptokurtic than that on the trait (Caballero and Keightley 1994; Lyman *et al.* 1996) because many mutants may not affect the trait under study substantially but are likely to affect fitness. In natural populations at mutation-selection balance (MSB), heterozygous mutants, which far outnumber the mutant homozygotes, are critical to maintenance of genetic variance. However, dominance coefficients of mutational effect are often assumed to be invariant, having a value of one-half (additive) in models of maintenance of quantitative genetic variation through MSB (Kimura 1965; Lande 1976; Turelli 1984; Barton 1990; Keightley and Hill 1990). The exception, to our knowledge, is the study of Caballero and Keightley (1994). They reviewed the data up to then of dominance coefficients of the mutational effects on fitness components (h) and metric traits (h') from Drosophila studies and took into account the varying dominance of mutations in a purely pleiotropic model. On the basis of investigations using a set of parameters obtained from their survey, they concluded that the equilibrium variance of the metric trait is "practically independent of the dominance" (Caballero and Keightley 1994, pp. 890 and 896). In a neutral model (Lynch and Hill 1986), dominance of mutations was also found to have little effect on genetic variance.

Theoretically, dominance comes as a consequence of the biochemical role played by a gene (Wright 1929; Haldane 1930; Kacser and Burns 1981). As Kacser and Burns (1981, p. 661) argued, "there is no inevitable identity of the effect of two alleles on the dominance index for a particular character and that for fitness, just as two pleiotropically related characters may have different dominance indices if they involve different pathways." Thus the situation where both h and h' are the same cannot be common. In fact, available experimental data suggested that h and h' are different and vary among loci (Mukai *et al.* 1972; Simmons and Crow 1977; Crow and Simmons 1983; Mackay *et al.* 1992; Lopez and Lopez-Fanjul 1993; Santiago *et al.* 1992; Lyman *et al.* 1996). For pure pleiotropic selection, the genetic load incurred by mutations is independent of the dominance (Haldane 1937). This is because the frequency of a deleterious mutant gene at MSB is $x \approx u/sh$ if $4Nhs \gg 1$ and selection is much stronger than the mutation rate u ($hs \gg u$; *cf.* Crow and Simmons 1983). Assuming mutations at all the mutable loci have the same s and h, the expected mean fitness of an outbred population at equilibrium is $W = \Pi_{i=1}^{n}(1 - 2x(1 - x)sh - x^2s) \approx \Pi_{i=1}^{n}(1 - 2u) \approx e^{-2\lambda}$, where $\lambda = \Sigma u$ is the haploid genome mutation rate. For the special case of $h' = \frac{1}{2}$ and $h > 0$, and all mutants having the same effect a on the trait as homozygotes, the genetic (additive) variance is approximated as $V_G = 2nx(1 - x)a^2/4 \approx \lambda a^2/(2hs)$ (*cf.* Barton 1990), which differs greatly from the conclusion of $V_G = \lambda a^2/s$ "for any degree of dominance" (Caballero and Keightley 1994, p. 889). This indeed shows that V_G is not in general independent of the dominance of mutations, and therefore it is necessary to investigate it more generally even in the pure pleiotropic model.

It is arguable that mutations that are (partially) recessive for fitness will segregate longer in the population and contribute more to the genetic variance than those that are additive. The total strength of apparent stabilizing selection may be affected little as it is determined mainly by real stabilizing selection (Zhang and Hill 2002). Thus, if the assumption of invariably additive mutations is relaxed, the joint-effect model will surely give different predictions for V_G and $V_{s,t}$. In this study we explore the extent to which dominance of mutations can help to account for the genetic variation maintained in a population at MSB. For convenience, the previous joint-effect model (Zhang and Hill 2002) is referred to as the *additive model* in the rest of this article.

MODEL AND METHODS

Gene action and contribution of mutations: A population of N diploid individuals, with random mating and at Hardy-Weinberg equilibrium, is assumed. It is also assumed that the mutation rate per locus is so low that at most two alleles are segregating per locus. Mutations in a diploid individual are assumed to have effects on a metric trait z, with a being the difference in value between homozygotes, and pleiotropic effects on fitness, with s being the difference in fitness between homozygotes. The haploid genome mutation rate is λ and the mutational variance in the quantitative trait is defined as $V_m = \frac{1}{2}\lambda E(a^2)$. There is neither linkage nor epistasis. Linkage disequilibrium between two segregating loci may be common but is unlikely to be an important factor as long as mutations remain at low frequencies in the majority of cases. Overdominance is also ignored. Although associative overdominance on some loci will appear due to a positive correlation in homozygosity between loci, it is significant only within populations with substantial inbreeding (Lynch and Walsh 1998; Charlesworth and Charlesworth 1999; Wang and Hill 1999).

Let the frequencies of the wild-type allele (A) and the mutant allele (a) at a given locus be $1 - x$ and x,

respectively, and so the frequencies of genotypes *AA*, *Aa*, and *aa* assuming Hardy-Weinberg proportions are $(1-x)^2$, $2x(1-x)$, and x^2. If the dominance coefficients of the mutational effect on the trait z and pleiotropic effect on fitness are h' and h, respectively, values for the trait z of the three genotypes are 0, ah', and a, and their pleiotropic effects on fitness are 1, $1-sh$, and $1-s$. Under the joint-effect model of pleiotropic and real stabilizing selection (Zhang and Hill 2002) with weak selection (mean fitness $\overline{W} = 1 - V_G/(2V_{s,r}) \approx 1$), the change in gene frequency resulting from one generation of selection is approximated as $\Delta x = -x(1-x)\bar{s}/2$ with the overall fitness effect

$$\bar{s} = 2s[h + (1-2h)x] + \frac{a^2}{4V_{s,r}}\{4h'^2 - 2x[1-(1-2h')^2(1-2x)^2 - 4(1-2h')(1+h')(1-x)]\}. \quad (1)$$

The genetic variance in the trait z affected by n independent loci is given as

$$V_G = \sum_{i=1}^{n} V_{G,i} \equiv \sum_{i=1}^{n} (V_{A,i} + V_{D,i}), \quad (2)$$

with the additive variance, $V_{A,i}$, and the dominance variance, $V_{D,i}$, contributed by locus i as

$$V_{A,i} = 2x_i(1-x_i)(a_i^2/4)[1 + (2h_i' - 1)(1-2x_i)]^2, \quad (3)$$

$$V_{D,i} = [a_i(2h_i' - 1)x_i(1-x_i)]^2 \quad (4)$$

(Falconer and Mackay 1996), respectively. The strength of apparent stabilizing selection can be measured as the regression of fitness on squared deviation of the trait value (z) from the optimum ($\bar{z}$) and evaluated as

$$V_{s,t} = -V_{G2}/[2\,\mathrm{Cov}(w, (z-\bar{z})^2)] \quad (5)$$

(Barton 1990; Keightley and Hill 1990; Zhang and Hill 2002).

In Equation 5, the covariance of relative fitness and squared deviation, $\mathrm{Cov}(w, (z-\bar{z})^2)$, can be partitioned into two parts: that due to real stabilizing selection, $V_{G2}/2V_{s,r}$, and that due to the pleiotropic effect on fitness, Cov_p, where

$$\mathrm{Cov}_p = -\sum_{i=1}^{n}[2x_i(1-x_i)h_is_i(\bar{z}_i - h_i'a_i)^2 + x_i^2s_i(\bar{z}_i - a_i)^2 - \bar{s}_iV_{G,i}]. \quad (6)$$

The variance of squared deviations can be decomposed as $V_{G2} = m_4 + 2V_G^2$ with the fourth moment under selection,

$$m_4 = \sum_{i=1}^{n}\{[(1-x_i)^2\bar{z}_i^4 + 2x_i(1-x_i)(\bar{z}_i - h_i'a_i)^4 + x_i^2(\bar{z}_i - a_i)^4] - 3V_{G,i}^2\}. \quad (7)$$

In the above expressions $\bar{z}_i = [(2h_i' - 1)(1-x_i) + 1]x_ia_i$ is the mean effect on the trait and $\bar{s}_i = [(2h_i - 1)(1-x_i) + 1]x_is_i$ is the mean pleiotropic effect on fitness of locus i.

Distributions of homozygous effects and dominance coefficients of new mutations: Although fine-scale information is still lacking, empirical data (Mackay *et al.* 1992; Keightley 1994; Lyman *et al.* 1996; García-Dorado *et al.* 1999; Garcia-Dorado and Caballero 2000; Chavarrias *et al.* 2001; Hayes and Goddard 2001; Mackay 2001) indicate that the distributions of effects of new mutations on both fitness and the metric trait are leptokurtic, and mutational effects on the trait are more leptokurtic than their pleiotropic effects are on fitness. As in previous studies (Keightley and Hill 1990; Zhang and Hill 2002), the distribution of mutational effects on the metric trait is assumed to be symmetrical about $a = 0$, and only deleterious mutations on fitness are assumed to occur, in accord with the classical view (Falconer and Mackay 1996). The effects of mutations, $|a|$ and s, were sampled from a gamma distribution or a function thereof: the "squared gamma distribution" and the "square-root gamma distribution," where, respectively, $\sqrt{s}$ and s^2, for example, have a gamma distribution (*cf.* Zhang *et al.* 2002). Note that the reflected square-root gamma ($\frac{1}{2}$) distribution is the normal (Gaussian) distribution. Here variants of the gamma distribution are employed to show that different distributions that possess the same variance and kurtosis can induce quite different predictions of V_G (see results below).

Dominance coefficients of new mutations are assumed to be either constant or variable across loci. Analyses of available experimental data suggest that dominance coefficients decrease with the size of homozygous mutational effects (Mukai *et al.* 1965; Simmons and Crow 1977; Charlesworth 1979; Lopez and Lopez-Fanjul 1993), and the mean dominance coefficient is distributed approximately as $\bar{h} = \exp(-Ks)/2$ (Caballero and Keightley 1994; Deng *et al.* 2002), which is in rough accord with the few available data (Mackay *et al.* 1992; Garcia-Dorado and Caballero 2000). As did Caballero and Keightley (1994), we assume dominance coefficients for the pleiotropic effect on fitness are uniformly distributed in the range $0 < h < \exp(-Ks)$, where the constant K is determined so that for a given distribution of s, the average dominance coefficient is $\bar{h}$. For example, if s follows a gamma (β_2) distribution with mean $\bar{s}_p$, then $K = (\beta_2/\bar{s}_p)[(2\bar{h})^{-1/\beta_2} - 1]$. Similarly, h' is assumed to be uniformly distributed in the range $0 < h' < \exp(-K'|a|)$. Further it is assumed that $h \le h'$ if the degree of dominance varies, as h and h' may be correlated (Caballero and Keightley 1994). In this study, the following methods are used to compute V_G and $V_{s,t}$, as mutual checks.

Single-locus Monte Carlo simulation: Although apparent stabilizing selection experienced by the trait acts on the alleles at all segregating loci, the above analysis

shows that its strength can be computed by summing the impact of each locus separately. Using the above basic expressions, we can simulate the process for each segregating mutant until its fixation in or loss from a population. For each new mutant with properties (a, h', s, h) sampled from a quadrivariate distribution $P(a, h', s, h)$ as described above, its initial frequency x_0 is set to $1/(2N)$, where N is the actual size of the population. We then calculate Equations 1–7. In the next generation, the expected mutant frequency is given by $x_1 = x_0 + \Delta x$ and the actual frequency is sampled from a binomial distribution with mean x_1 (Press *et al.* 1989). Equations 1–7 are recalculated and values of V_A, V_D, m_4, and Cov_p are added to those of the previous generation to compute the lifetime contributions. The process continues until the actual frequency or its expectation reaches the bound 0 or 1. A large number of mutants (*e.g.*, 10^8) were sampled and the averages of all those quantities were taken and then multiplied by $2\lambda N$ (the expected number of new mutations each generation) to obtain expected values of V_G, V_D, m_4, Cov_p, and $V_{s,t}$ at the steady state of accumulation and loss of mutations.

Individual-based Monte Carlo simulation: As a check for the above single-locus simulation, a multiple-locus and individual-based simulation procedure, modified from Keightley and Hill (1983, 1988), was used. The population was started from an isogenic state and allowed to reach equilibrium by ignoring the first $6N$ generations. Each generation the sequence of operations was mutation, selection, mating, and reproduction. The fitness of individual i was assigned as $w_i = 1 - [\sum_j s_{ij} + (z_i - \bar{z})^2/2V_{s,r}]$ where $z_i = \sum_j a_{ij}$ is the value of the trait and $\bar{z}$, the population mean of the trait, approximates the optimum. If $0 < w_i \leq 1$, then the chance that individual i was chosen as a parent of the next generation was proportional to w_i; if $w_i \leq 0$, it had no offspring. It should be noted that the population generated by this scheme of selection maintains mean fitness around a constant value from generation to generation, comparable with Haldane's (1937) law, *i.e.*, $\exp(-2\lambda)$ for large populations, whereas in the model of Keightley and Hill (1983, 1988) mean fitness always keeps falling. For each generation of the equilibrium population, V_G, V_{G2}, and $\mathrm{Cov}(w, (z - \bar{z})^2)$ were computed and averaged to estimate their means.

Diffusion approximations: Kimura's (1969) diffusion theory was applied under the infinite independent loci model. Assuming no epistasis, the density function of the stationary distribution of allele frequency at MSB, $\phi(x)$, is given by Equation 37 of Kimura (1969). In contrast to Kimura (1969), here the overall selective coefficient $\tilde{s}$ of a mutant depends on its frequency, dominance coefficients, the trait effect, and the pleiotropic effect on fitness (see Equation 1). The expectation I_f of an arbitrary function $f(x)$ with respect to the equilibrium distribution $\phi(x)$ was obtained by integration of Equation 18 of Kimura (1969). As in Caballero and Keightley (1994), mutational effects were sampled from $P(a, h', s, h)$, and the equilibrium value of $f(x)$ assuming no overdominance was obtained by integration of

$$\int_{-\infty}^{\infty}\int_{0}^{1}\int_{0}^{\infty}\int_{0}^{1} I_f P(a, h', s, h)\, da dh' ds dh. \quad (8)$$

Monte Carlo integration was used to compute Equation 8.

ANALYTIC APPROXIMATIONS FOR INFINITE POPULATION

If the population size is large and mutations are not completely recessive or neutral (*i.e.*, $hs > 0$ or $h'|a| > 0$) such that $2NE(\tilde{s}) \gg 1$, mutant frequencies then remain very low and items of $O(x^3)$ or higher in Equations 1, 3, 6, and 7 can be ignored, reducing to

$$\tilde{s} = 2sh + (2h'a)^2/4V_{s,r} \quad (9)$$

$$V_G = \sum_{i=1}^{n} 2x_i(1 - x_i)(2h_i'a_i)^2/4 \quad (10)$$

$$\mathrm{Cov}_p = -\sum_{i=1}^{n} 2x_i(1 - x_i)(1 - 2x_i)(2h_is_i/2)(2h_i'a_i)^2/4 \quad (11)$$

$$m_4 = \sum_{i=1}^{n} 2x_i(1 - x_i)(2h_i'a_i)^4/16. \quad (12)$$

With this rare allele assumption, only the heterozygous effects of mutants, hs and $h'a$, are relevant to the genetic processes that control the equilibrium genetic variance. If $2NE(\tilde{s}) \gg 1$, diffusion theory shows that the asymptotic expectations of the functions $2x(1 - x)$ and $2x(1 - x)(1 - 2x)$ approach $4\lambda/\tilde{s}$ (Kimura 1969; Zhang *et al.* 2002). Thus the genetic variance V_G, the covariance of relative fitness and squared deviation due to pleiotropic effect Cov_p, and the fourth moment under selection m_4 can be calculated through expression (8) using $I_f = 4\lambda V_{s,r}[(2h'a)^2/4V_{s,r}]/\tilde{s}$, $I_f = 4\lambda V_{s,r}(2hs/2)[(2h'a)^2/4V_{s,r}]/\tilde{s}$ and $I_f = 4\lambda[(2h'a)^4/16]/\tilde{s}$, respectively. These quantities are evaluated by Monte Carlo integration (*e.g.*, Keightley and Hill 1990). Compared with the additive model (Zhang and Hill 2002), all else being the same, the equilibrium genetic variance V_G decreases if $h > h'$ and increases if $h < h'$, as expected intuitively. In fact, the strength of apparent stabilizing selection can be simplified as

$$V_{s,t} = V_{s,r}[1 - \mathrm{Cov}_p/(V_G^2/V_{s,r} + (2h')^2V_m)] \quad (13)$$

or

$$V_{s,t}^{-1} = V_{s,r}^{-1} + V_{s,p}^{-1} \quad (14)$$

(*cf.* Zhang and Hill 2002, Appendix A), where the strength of apparent stabilizing selection due to pleiotropic effects is

$$V_{s,p} = [V_G^2 + ((2h')^2V_M - \mathrm{Cov}_p)V_{s,r}]/\mathrm{Cov}_p. \quad (15)$$

Since $\mathrm{Cov}_p < (2h')^2V_M$ (Zhang and Hill 2002), $V_{s,p} >$

$V_G^2/(2h')^2V_M$, suggesting that whenever the genetic variance is close to the observed levels, the stabilizing selection due to pleiotropic effects of mutations is quite weak, in agreement with the pure pleiotropic model (Barton 1990; Zhang *et al.* 2002). As the asymptotic expectation of $[x(1-x)]^2$ vanishes when $N \to \infty$ (Kimura 1969), the dominance variance vanishes due to the fact that almost all segregating mutant alleles are in heterozygotes. Thus additive variance comprises most of V_G within a large population.

If dominance coefficients are constant across loci, algebraic expressions for V_G and $V_{s,t}$ can be obtained for some distributions of mutational effects (*cf.* Table 1 of Zhang and Hill 2002). For instance, if the squared effect on the trait (a^2) and the pleiotropic effect on fitness (s) of mutations follow independent gamma (β_1) and gamma ($\beta_2 = 1 - \beta_1$) distributions, respectively, then

$$V_G = 4\lambda V_{s,r}(1-\theta^{1-\beta_2})/(1-\theta), \tag{16}$$

$$V_{s,t} = V_{s,r}\{1-(2h')^2V_m(\beta_2+\beta_1\theta^2-\theta^{2-\beta_2})/[\beta_1(1-\theta)^2 \times (V_G^2/V_{s,r}+(2h')^2V_m)]\}. \tag{17}$$

(see Appendix). In Equations 16 and 17 $\theta \equiv (2h\bar{s}_p/\beta_2)/((2h')^2\bar{s}_r/\beta_1)$, $\bar{s}_p$ denotes the mean homozygous pleiotropic effect on fitness, and $\bar{s}_r \equiv E(a^2/4V_{s,r}) = 2V_m/(4\lambda V_{s,r})$ represents the mean selection coefficient arising from real stabilizing selection on homozygous mutational effects on the trait. If the two dominance coefficients h and h' are the same, the genetic variance V_G increases with dominance coefficients whereas $V_{s,t}$ decreases. However, if all mutations are additive for the trait (*i.e.*, $h' = 0.5$), both V_G and $V_{s,t}$ increase as h decreases, and at the extreme situation of $h = 0$, the house-of-cards approximations hold: $V_{s,t} = V_{s,r}$ and $V_G = 4\lambda V_{s,r}$ (Turelli 1984). This shows that even though pleiotropic effects on the carriers of the mutations when homozygous occur in principle, the population experiences little pleiotropic selection as real stabilizing selection is effective in keeping recessive mutants rare and thus heterozygous. In the other extreme case where pleiotropic effects on fitness follow the geometric distribution (Hill 1982b; *i.e.*, $\beta_2 \to 0$), Equations 16 and 17 also return to the house-of-cards approximations, reflecting the fact that most mutants have little effect on fitness. It should be noted that varying dominance coefficients across loci as described above increases the predictions of V_G and $V_{s,t}$, especially for more recessive mutants for fitness (*cf.* Table 1 and Figure 3 below).

NUMERICAL RESULTS

Monte Carlo simulation methods are employed to illustrate the dependence of both V_G and $V_{s,t}$ on the population size, to verify the above analytical approximations in a large population when $2NE(\bar{s}) \gg 1$ and, using single-locus simulation, to show how the dependence of V_G on the degree of dominance of genes is affected by population size. For other cases, diffusion approximations are used to save computation time. Our aim is to display quantitatively what differences the variable dominance and the exact shape of distributions of mutational effects cause to the predictions of V_G and $V_{s,t}$.

Dependence of V_G and $V_{s,t}$ on the population size: As natural populations may not be sufficiently large and the distribution of mutational effects is highly leptokurtic such that $2NE(\bar{s}) \gg 1$ may not hold for some mutant genes, it is relevant to investigate the influence of N on the predictions of V_G, V_D, and $V_{s,t}$. Diffusion approximations with single-locus and individual-based Monte Carlo simulation results are shown in Figure 1, where the results from different methods are in good agreement. As the population size N increases, V_G and $V_{s,t}$ increase and approach asymptotic values predicted by analytical approximations, while V_D increases to a peak and then decreases and vanishes, although larger population sizes are required to approach infinite approximations when mutational effects become more leptokurtic. The trend of dependence of V_G and $V_{s,t}$ on N is similar to that for the additive model (Figure 4 of Zhang and Hill 2002); but, as expected, it is quite different from that of the purely pleiotropic model (*cf.* Figure 4 of Caballero and Keightley 1994). In the following, except where stated otherwise, we consider large populations such that $2NE(\bar{s}) \gg 1$ holds and thus analytical approximations apply.

Influence of dominance on V_G and $V_{s,t}$: This is shown in the following three different situations.

Dominance coefficients equal and constant: Consider the situation where dominance coefficients for the pleiotropic effect on fitness and for the trait are the same, *i.e.*, $h = h'$, and remain constant across loci. The results in Figure 2 show that the genetic variance V_G increases with the dominance coefficients, but that the increase in V_G is not large, in agreement with the prediction of Caballero and Keightley (1994). The value of $V_{s,t}$ decreases as the degree of dominance of mutants increases; *i.e.*, the apparent stabilizing selection becomes stronger, but more slowly so as the kurtosis of s increases. The results indicate that with dominant mutations, only a slightly higher V_G is maintained under relatively strong apparent stabilizing selection, compared to additive mutant genes.

Dominance coefficients different and constant: Results are shown in Figure 3, a and b (dotted curves), for the case where mutant genes are assumed to be additive for the trait ($h' = 0.5$). Both V_G and $V_{s,t}$ decrease with increasing degree of dominance of the pleiotropic effect (h). Intuitively, this is because, with increasing h, selection becomes more effective in removing mutant genes from the population, thus reducing mutant frequencies. As the rate of mutation decreases, real stabilizing selection

becomes significant in relation to pleiotropic selection (*cf.* Figure 3 of Zhang and Hill 2002) and V_G becomes nearly independent of h over a larger range. With an increasing rate of mutation, however, real stabilizing selection becomes weak and V_G becomes increasingly affected by h. Thus high levels of V_G can be maintained and apparent stabilizing selection is due mainly to real stabilizing selection, as mutants for pleiotropic effect on fitness become more recessive.

Variable dominance coefficients: For the case where dominance coefficients h and h' vary across loci as described in model and methods, the results are shown in Figure 3, a and b (solid curves), and Table 1. Comparison with constant dominance coefficients (dotted curves, fixing h at $\bar{h}$ and h' at 0.5) displays that, all else being the same, varying dominance coefficients increases V_G and $V_{s,t}$ (*i.e.*, reduces apparent stabilizing selection). This is due to the assumption that the dominance coefficients are inversely correlated with mutational effects so that the heterozygous effects of mutations on fitness (hs) always remain small, resulting in a relatively weak selection. Moreover, all mutant genes become mildly deleterious when heterozygous and thus segregate for a long time in the population and reach higher frequencies, so that the genetic variance increases. Dominance variance appears as h' fluctuates around the mean 0.5, but the value of V_D is very small, <1% of V_G. Given $\bar{h}' = 0.5$, V_G increases rapidly and approaches the house-of-cards approximation $V_G = 4NV_{s,r}$ (Turelli 1984) as $\bar{h}$ reduces to nil. Consider typical estimates of parameters $\bar{s}_P = 0.1$, $\lambda = 0.1$, $V_m = 10^{-3}V_E$, and $\bar{h} = 0.1$ (Lynch *et al.* 1999; Garcia-Dorado and Caballero 2000; Carr and Dudash 2003; García-Dorado *et al.* 2003) with a and s following a reflected gamma (0.0847) and gamma (½) distributions, respectively. Variable dominance coefficients result in $V_G = 1.89V_E$, over 15 times that for the additive model ($0.12V_E$) (Zhang and Hill 2002), while the strength of apparent stabilizing selection is reduced by only 50% (from $12.1V_E$ to $19.9V_E$, see Table 1). However, as $\bar{h}$ increases and exceeds 0.3, V_G and $V_{s,t}$ become roughly independent of $\bar{h}$, which partly reflects the constraint $h \le h'$ used in the calculations.

If mutations for the trait are exclusively additive, a negligible increase in V_G and a slight increase in $V_{s,t}$ occur, compared to the above where h' varies. Further, removing the constraint $h \le h' = 0.5$ on variable domi-

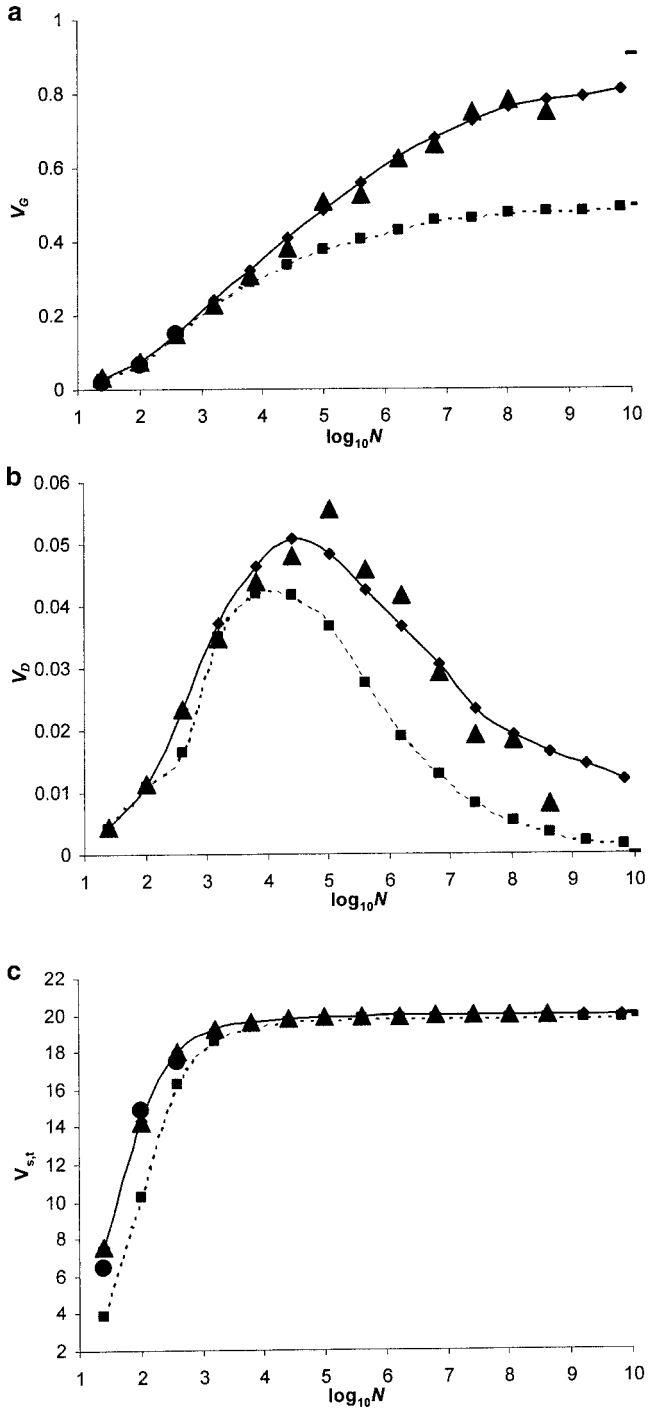

Figure 1.—Equilibrium genetic (V_G) (a) and dominance variance (V_D) (b) and the strength of apparent stabilizing selection ($V_{s,t}$) (c), plotted against population size (N) for mutational effects of variable dominance coefficients with means $\bar{h} = 0.2$ and $\bar{h}' = 0.2$. Mutational effects on both the trait and fitness are independent, homozygous pleiotropic effects on fitness follow a gamma (0.125) distribution (kurtosis = 47.2), and homozygous effects on the trait a reflected gamma (0.0846) distribution (kurtosis = 70). Typical estimates of mutation and selection parameters are assumed: the mutation rate $\lambda = 0.1$ per haploid genome per generation, mean pleiotropic effect on fitness $\bar{s}_p = 0.1$, mutational variance $V_m = 10^{-3}V_E$, and real stabilizing selection of strength $V_{s,r} = 20V_E$. Single-locus simulation results (triangle) are obtained by averaging over 10^8 mutation events, and individual-based simulations (circles) are obtained assuming 10^3 mutable loci and averaging over 10^3 equilibrium generations. Diffusion results (diamond) are obtained by Monte Carlo integration over 10^5 samples; the curves are the solid lines through the diffusion data. The dash at the end of curves represents the infinite population approximation, which is approached on the diffusion results (*e.g.*, $V_G = 0.9V_E$ for $N = 10^{13}$). The dashed curves are obtained by diffusion approximation for a and s following independent reflected gamma (0.196) and gamma (0.25) distributions, respectively.

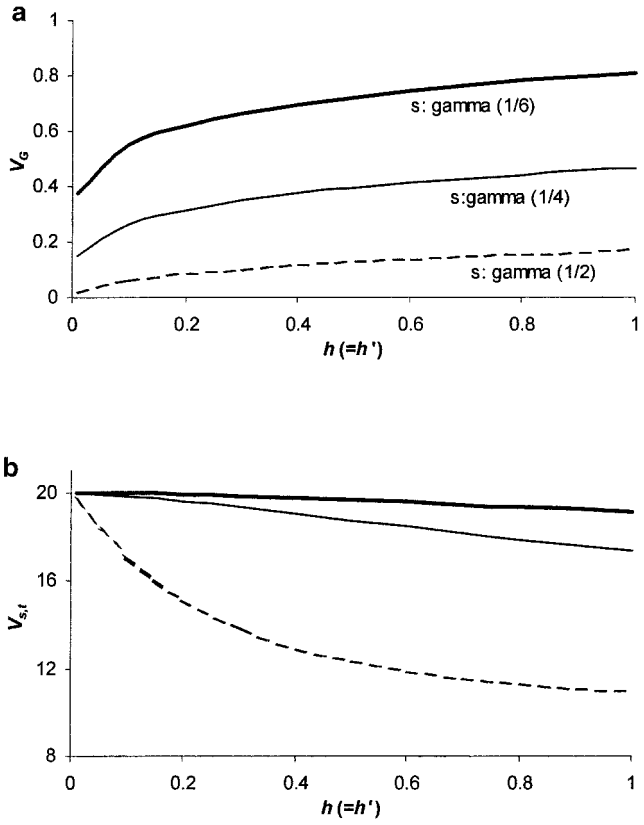

FIGURE 2.—Influence of dominance coefficients of mutations on the genetic variance (a) and the strength of apparent stabilizing selection (b). Dominance coefficients for fitness and for the trait are assumed to be the same and constant across loci. Mutational effects on the trait follow a reflected gamma (0.091) distribution (kurtosis = 65), while pleiotropic effects of mutations are distributed as gamma (⅙), gamma (¼), or gamma (½) with kurtosis 35.3, 23.4, 11.7, respectively. Other parameters of mutation and selection are as in Figure 1 (*i.e.*, $\lambda = 0.1$, $V_m = 10^{-3}V_E$, $\bar{s}_p = 0.1$, and $V_{s,r} = 20V_E$).

nance coefficients results in a minor decrease in $V_{s,t}$ and a slight decrease in V_G. If $\bar{h}' < 0.5$, all else being the same, the prediction of V_G is smaller and that of $V_{s,t}$ is larger than those for $\bar{h}' = 0.5$. However, such changes in V_G and $V_{s,t}$ due to a decrease in $\bar{h}'$ are not large if the deviation of $\bar{h}'$ from 0.5 is small (*cf.* CABALLERO and KEIGHTLEY 1994). For example, with $\bar{h}' = 0.4$, the decrease in V_G is <10% when $\bar{h} = 0.1$ and shrinks rapidly as $\bar{h}$ becomes smaller, while the increase in $V_{s,t}$ is <1% (see Figure 3, a and b).

Impact of distributions of mutational effects on V_G and $V_{s,t}$: The results listed in Table 1 show that under the constraint $k_4(a) > k_4(s)$, even the additive model can generate abundant genetic variance with highly leptokurtic mutational effects. Here values of the kurtosis $k_4(a) \equiv E(a^4)/E(a^2)^2$ and $k_4(s) \equiv E(s^4)/E(s^2)^2$ are intended to describe the shape of distributions of mutational effects. If mutational effects on the trait follow a reflected squared exponential distribution with kurtosis $k_4(a) = 70$, for example, V_G can increase dramatically from 0.19 to 0.69 when the distribution of pleiotropic effects changes from gamma (½) to gamma (¼). Data in Table 1 further show how different assumptions for distributions of mutational effects change the predictions of V_G and $V_{s,t}$. The three distributions of mutational effects on the trait, reflected square-root gamma (0.0145), reflected gamma (0.0847), and reflected squared exponential, for example, have the same kurtosis $k_4(a) = 70$. However, they give very different predicted values of V_G, 0.22, 0.38, and 0.69 when $h = 0.5$, and 3.67, 4.70, and 5.79 when $\bar{h} = 0.1$, if the pleiotropic effects on fitness are assumed to have a gamma (¼) distribution. The change in $V_{s,t}$ is comparatively small, however. This implies that the assumption of the squared gamma distribution actually allows more mutants of large effect on the trait than do the other two distributions, and different distributions of a give different predictions of V_G. Therefore, a description of the distribution solely in terms of kurtosis is not sufficient.

If the population size is not sufficiently large to retain $2NE(\bar{s}) \gg 1$ for most genes, predictions of the genetic variance maintained, which are calculated using formulas for infinite population size, blow up. Considering a population size of 10^5, the predicted value of V_G is the same as or slightly smaller than the infinite approximation if constant dominance coefficients are assumed (Figure 2 and Table 1). For the variable dominance case, the predicted value of V_G decreases rapidly as $\bar{h}$ is reduced, but that of $V_{s,t}$ remains roughly the same (see Figure 3, c and d, and Table 1). For a population of this size, the increase in V_G relative to the additive case, >60% for $\bar{h} = 0.2$ and >90% for $\bar{h} = 0.1$, is substantial (see Table 1), and the dependence of V_G on dominance still holds, although it is somewhat weaker (see also Figure 3c). Results in Figure 3c and Table 1 for finite population sizes show that for typical estimates of mutation and selection parameters, wherever $k_4(s) < k_4(a) < 10k_4(s)$, variable dominance coefficients increase the prediction of V_G to the levels observed in natural populations.

Impact of the correlation between $|a|$ and s on V_G and $V_{s,t}$: It is biologically plausible that mutational effects on the trait and fitness are correlated (see KEIGHTLEY and HILL 1990). If the marginal distributions of a and s have quite different degrees of kurtosis, effects of mutations on the trait and on fitness can be only partially correlated (WHITTAKER 1974). For a fitness-related trait such as life history, the difference between $k_4(a)$ and $k_4(s)$ is likely to be smaller than that for a trait less directly related to fitness, *e.g.*, morphology. Figure 4 shows the influence of the correlation coefficient, $\rho = \mathrm{cov}(|a|, s)/\sqrt{V[|a|]\,V[s]}$, between $|a|$ and s on both V_G and $V_{s,t}$. As h decreases or the difference between $k_4(a)$ and $k_4(s)$ increases, the impact of the correlation on V_G becomes large while its impact on $V_{s,t}$ becomes small. However, it can still be concluded, as in the additive model (ZHANG and HILL 2002), that if the correlation between

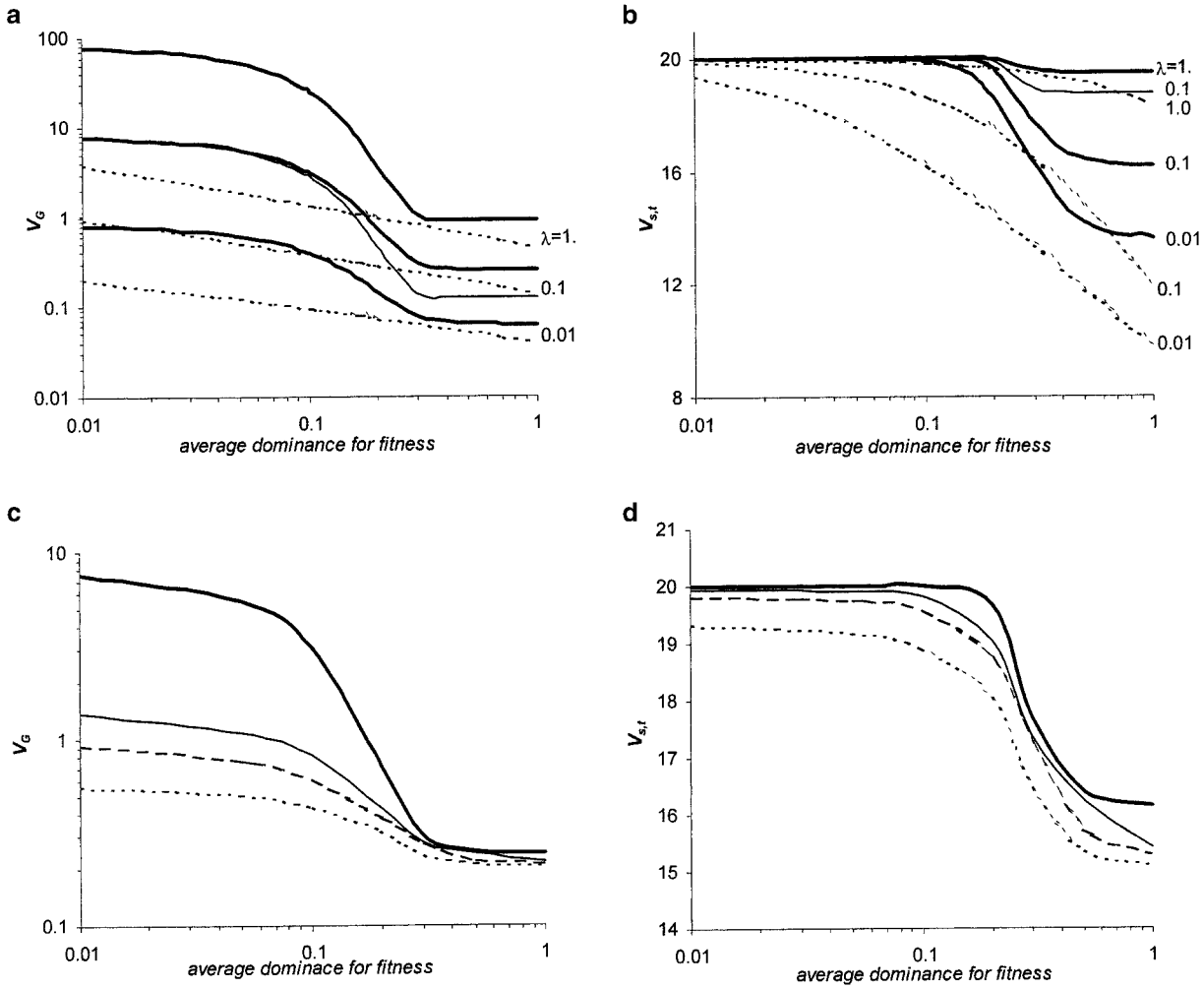

FIGURE 3.—Influence of dominance coefficients of mutations on the genetic variance (a and c) and the strength of apparent stabilizing selection (b and d). The distributions of homozygous mutational effects are assumed to be reflected squared exponential for a and gamma (½) for s. The x-axis is the average dominance coefficient for pleiotropic effects of mutations on fitness. (a and b) Results are shown assuming infinite population size for three genome-wide mutation rates. Dotted curves are results for constant dominance coefficients (*i.e.*, $h = \bar{h}$, and $h' = 0.5$); solid thick curves are for variable dominance coefficients as described in the text with means $\bar{h}$ and $\bar{h}' = 0.5$; and solid thin curves are for variable dominance coefficients with means $\bar{h}$ and $\bar{h}' = 0.4$ and mutation rate $\lambda = 0.1$. Other parameters of mutation and selection are as in Figure 1 (*i.e.*, $V_m = 10^{-3}V_E$, $\bar{s}_p = 0.1$, and $V_{s,r} = 20V_E$). (c and d) Comparison of results between infinite populations (solid curves) and finite populations of $N = 10^6$, 10^5, and 10^4 (solid thin, dashed, and dotted curves, respectively, obtained by single-locus Monte Carlo simulation) for $\bar{h}' = 0.5$, $\lambda = 0.1$.

$|a|$ and s is at most intermediate, its influence on V_G and $V_{s,t}$ is not large.

DISCUSSION

Predictions of genetic variance (V_G) and strength of apparent stabilizing selection ($V_{s,t}$) at mutation-selection balance depend not only on the mean and variance of mutational effects but also on the exact shapes of their distributions. The additive version of the joint-effect model of continuously varying mutational effects (ZHANG and HILL 2002) can induce a significant amount of stabilizing selection as well as a substantial genetic variance when the distribution of pleiotropic fitness effects is more leptokurtic than that of effects on a trait. It is intuitively plausible, however, that most mutations affect fitness in one way or another, but many fewer may affect a particular metric trait (especially when it is not closely related to fitness). This suggests that genome-wide mutations must have a much more leptokurtic distribution of their effects on a metric trait than on fitness. Extending the additive model (ZHANG and HILL 2002) by including dominance of mutations, we show that when mutations are much more recessive for fitness than for a metric trait of interest, high levels of genetic variance under strong stabilizing selection can be maintained under realistic assumptions for mutations.

Most mutants of sufficiently large effect that their degree of dominance can be estimated are recessive or nearly so for fitness (FISHER 1928; MULLER 1950; LYNCH

TABLE 1

Influence of leptokurtosis and dominance of mutations on V_G and $V_{s,t}$

Distribution of $\lvert a\rvert$			Distribution of s		Infinite population					Population size 10^5				
					$h = h' = 0.5$		$\bar{h} = 0.2, \bar{h}' = 0.5$		$\bar{h} = 0.1, \bar{h}' = 0.5$:	$h = h' = 0.5$		$\bar{h} = 0.2, \bar{h}' = 0.5$		$\bar{h} = 0.1, \bar{h}' = 0.5$:
	β_1	$k_4(a)$	β_2	$k_4(s)$	V_G	$V_{s,t}$	V_G	$V_{s,t}$	V_G	V_G	$V_{s,t}$	V_G	$V_{s,t}$	V_G
Square-root gamma (β_1)	0.5	3	0.5	11.7	0.38	17.8	1.40	19.8	4.31	0.38	17.8	0.80	19.4	1.38
	0.125	9	0.875	6.7	0.09	7.2	0.35	17.7	1.40	0.09	7.1	0.29	16.5	0.60
	0.0313	33	0.9687	6.2	0.06	5.5	0.18	15.5	0.54	0.06	5.8	0.16	14.7	0.30
	0.0145	70	0.9855	6.1	0.04	6.0	0.12	15.1	0.31	0.04	5.8	0.11	14.5	0.19
			0.5	11.7	0.09	10.3	0.26	18.7	1.03	0.09	10.4	0.18	17.5	0.28
			0.25	23.4	0.22	16.3	0.94	19.9	3.67	0.19	16.9	0.32	19.3	0.40
	0.0055	184	0.9945	6.0	0.03	8.1	0.07	15.8	0.15	0.03	7.9	0.06	15.7	0.10
			0.5	11.7	0.05	10.8	0.13	18.4	0.48	0.05	10.5	0.10	17.6	0.14
			0.25	23.4	0.11	14.3	0.44	19.9	2.56	0.10	14.6	0.16	19.0	0.20
Gamma (β_1)	0.0847	70	0.5	11.7	0.12	12.1	0.41	19.3	1.89	0.12	12.1	0.26	18.1	0.41
			0.25	23.4	0.38	18.2	1.67	19.9	4.70	0.33	18.6	0.52	19.6	0.66
	0.0324	184	0.5	11.7	0.07	11.4	0.22	18.8	1.03	0.07	10.9	0.15	17.7	0.23
			0.25	23.4	0.19	16.2	0.92	19.97	3.72	0.17	16.9	0.27	19.3	0.36
Squared gamma (β_1) distribution	1.0	70	0.5	11.7	0.19	14.3	0.72	19.7	3.13	0.18	14.7	0.38	18.7	0.64
			0.25	23.4	0.69	19.3	2.76	20.0	5.79	0.55	19.5	0.88	19.8	1.12
	0.5	184	0.5	11.7	0.13	13.3	0.49	19.5	2.52	0.13	13.1	0.25	18.7	0.41
			0.25	23.4	0.48	18.8	2.19	20.0	5.28	0.39	19.2	0.57	19.7	0.75

Typical estimates of mutation and selection parameters are used: $\lambda = 0.1$, $\bar{s}_p = 0.1$, $V_m = 10^{-3}V_E$, and $V_{s,r} = 20V_E$. Pleiotropic effects on fitness of mutations are assumed to follow gamma distributions while three different types of distribution are assumed for mutational effects on the quantitative trait. Results are shown for three different dominance coefficients that are either constant or variable as described in the text. Values of $V_{s,t}$ for $\bar{h} = 0.1$ and $\bar{h}' = 0.5$ (not listed) are slightly smaller than $20V_E$ ($19.3V_E < V_{s,t} < 20V_E$). Results for infinite population sizes obtained from the diffusion approximation and those for population size $N = 10^5$ were obtained by single-locus Monte Carlo simulation.

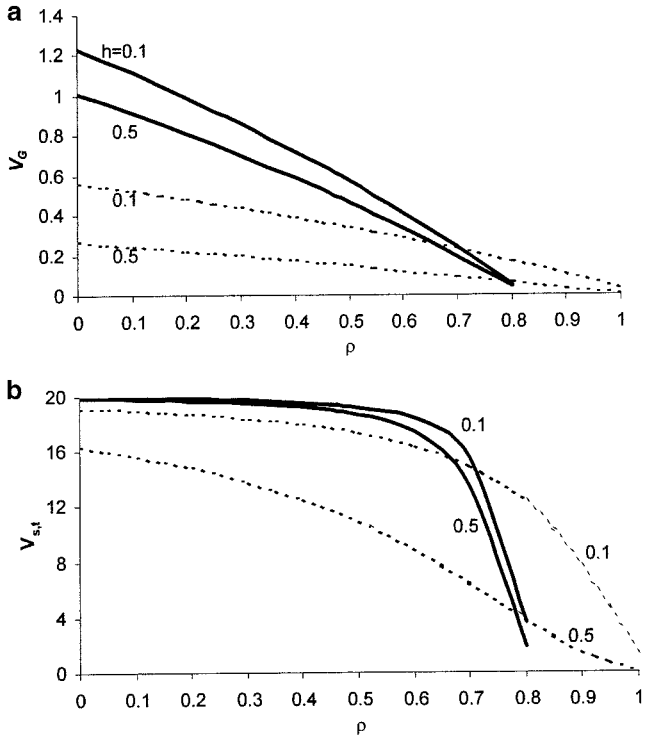

FIGURE 4.—Influence of the correlation between the absolute value of mutational effects on the trait and the pleiotropic effect on fitness on V_G (a) and $V_{s,t}$ (b). Two different distributions for a and s are considered: a Wishart distribution (dashed curves) and a bivariate gamma distribution with marginal gamma (0.0847) distribution for $|a|$ and marginal gamma (0.125) distribution for s. Mutational effects on the trait are additive while dominance coefficients for the pleiotropic effect on fitness are 0.5 and 0.1, shown beside the curves. Only constant dominance coefficients are considered. Other parameters of mutation and selection are as in Figure 1 (*i.e.*, $\lambda = 0.1$, $V_m = 10^{-3}V_E$, $\bar{x}_p = 0.1$, and $V_{s,r} = 20V_E$).

and WALSH 1998), as is expected under certain metabolic models (KACSER and BURNS 1981; KEIGHTLEY 1996). Further, experimental data have shown that dominance coefficients of mutant alleles vary among loci as do their effects, and highly deleterious mutations tend to be nearly recessive (MUKAI *et al.* 1972; SIMMONS and CROW 1977; CHARLESWORTH 1979; CROW and SIMMONS 1983; MACKAY *et al.* 1992; CABALLERO and KEIGHTLEY 1994). Considerations of (partially) recessive mutations have lent support to the explanations for many phenomena, such as Haldane's rule that when only one sex in a cross-species hybrid is sterile, it is usually the heterogametic sex (TURELLI and ORR 1995), the bottleneck effect on genetic variance (WANG *et al.* 1998), and maintenance of sex (CHASNOV 2000; AGRAWAL and CHASNOV 2001). However, dominance has usually been ignored in models of genetic variation (KIMURA 1965; LANDE 1976; TURELLI 1984; BARTON 1990; KEIGHTLEY and HILL 1990). A simple analysis in the pure pleiotropic model confirms that V_G indeed depends on the dominance coefficient. Detailed analysis of the joint-effect model of real stabilizing selection and pleiotropic selection also indicates that dominance of mutants can substantially affect predictions of V_G and $V_{s,t}$, depending particularly on their relative degree of dominance on the metric trait and on the pleiotropic effect on fitness. In particular, mutants that are much more recessive for the pleiotropic fitness effect produce higher levels of V_G, while their influences become small if values of h and h' are the same or quite similar (see Figures 2 and 3; *cf.* CABALLERO and KEIGHTLEY 1994).

As is the case for measurements of other important parameters of mutation (*e.g.*, mutation rate and effect), estimates of dominance coefficients are imprecise (LYNCH *et al.* 1999; GARCÍA-DORADO *et al.* 2003) and may differ dramatically between segregating and new mutations (LYNCH and WALSH 1998; VASSILIEVA *et al.* 2000; CHAVARRIAS *et al.* 2001). In a recent review, GARCÍA-DORADO *et al.* (2003) suggest a mean dominance coefficient of the order of 0.2 for new mutations from published estimates of mean dominance coefficients of mutations on viability and other life-history traits in *D. melanogaster* and *C. elegans*. Although viability and other life-history traits are certainly related to *overall* fitness in one way or another, the relationship between them is obviously neither simple nor direct. In theory, effects of mutant genes should be more recessive on overall fitness than on its components (KACSER and BURNS 1981; DEAN *et al.* 1989). It is thus likely that the mean dominance coefficient for overall fitness is <0.2 and probably ~ 0.1 (SIMMONS and CROW 1977; HOULE *et al.* 1997; LYNCH and WALSH 1998; GARCIA-DORADO and CABALLERO 2000; VASSILIEVA *et al.* 2000; CARR and DUDASH 2003; FRY and NUZHDIN 2003; PETERS *et al.* 2003).

The available data from *P*-element insertions (MACKAY *et al.* 1992; LYMAN *et al.* 1996) suggest that the dominance coefficient for fitness is less than that for the metric trait. Although *P*-element insertions are different from spontaneous mutations in many aspects, there is good reason to believe that properties of *P*-element insertions to some extent resemble those of naturally occurring mutations (LYMAN *et al.* 1996). Furthermore, FRY and NUZHDIN (2003) found that transposable element insertions have greater average dominance in their viability effects than do point mutations due to a direct effect of heterozygous transposable element expression on fitness, suggesting that spontaneous mutations should have smaller dominance than transposable element insertions. Available data are rare, but the survey by CABALLERO and KEIGHTLEY (1994) suggests a relationship between dominance coefficients of mutants with extreme effects on fitness and on the bristle trait in Drosophila, $h \approx 0.4\,h'$. Metabolic control theory suggests that, in the absence of saturation and feedback or other nonlinearities, traits should have the same degree of dominance (KEIGHTLEY and KACSER 1987), but those assumptions seem too simplistic if overall fitness is one of the traits (KACSER and BURNS 1981). For a quantitative

trait that is not closely related with fitness, mutational effects on it are likely to be directly associated with the mutants and thus can be expressed directly and more or less additively. For fitness the expression of mutational effects relies on more complicated and indirect multiple pathways and thus appears to be more recessive. These data and reasoning, albeit inconclusive, seem to suggest that mean dominance coefficients of the order $\bar{h} \sim 0.1$ and $\bar{h}' \sim 0.5$ are likely for new mutations in natural populations, but more experimental work is required. Treating h as a constant or as varying randomly in the range $[0, \exp(-Ks)]$ with mean $\bar{h}$ (Caballero and Keightley 1994) gives rise to different predictions of V_G and $V_{s,t}$. Varying h increases V_G and $V_{s,t}$, and the present model can still produce high levels of genetic variance even for $\bar{h} \sim 0.2$ and $\bar{h}' \sim 0.4$ (see Table 1 and Figure 3).

The degree of leptokurtosis of pleiotropic effects of mutations can also affect the predicted value of V_G (see Table 1). Recessivity reduces the effective value of the pleiotropic effect on fitness (*i.e.*, hs) while its leptokurtosis increases the fraction of nearly neutral mutant genes, and both reduce pleiotropic selection and generate large V_G and $V_{s,t}$. Whenever V_G is up to the observed levels, apparent stabilizing selection is determined mainly by real stabilizing selection (*i.e.*, $V_{s,t} \sim V_{s,r}$; see Table 1). Given the variance and the kurtosis of the distribution of a, reducing the actual fraction of nearly neutral mutants for the trait can, however, also significantly increase the prediction of V_G but slightly increase $V_{s,t}$. All those observations confirm the conclusion that most V_G produced in the joint-effect model comes from the alleles that are nearly neutral for fitness in heterozygotes and most $V_{s,t}$ is contributed by the alleles that have large effects on the trait (Barton 1990; Zhang and Hill 2002).

The assumptions of highly leptokurtic distributions of homozygous effects and of the inverse relationship between the degree of dominance and homozygous effects imply that a large fraction of deleterious mutations have very small effects, such that there is very weak selection against most newly arising mutations. For the infinite approximation for V_G to hold (see Figure 1), it requires a very large population, but this is not the case for some natural populations, especially of large vertebrates. The present model, however, shows that V_G still depends on dominance for reasonable population sizes (*e.g.*, 10^4, 10^5), albeit more weakly so, and predicts a high equilibrium genetic variance (see Figures 1 and 3c and Table 1).

One check of the joint-effect model of genetic variation presented here is whether the random-mating population at MSB can survive the inbreeding depression due to an alteration of mating system, for example, full-sib mating. Inbreeding results in an increase in homozygosity and in the fixation probability of deleterious mutants, leading to increased mutational load, decreased fitness, and thus a potentially higher risk of extinction of the population (Falconer and Mackay 1996). Assuming the dominance coefficient of mutations for the pleiotropic effect on fitness is $h < 0.5$ across loci while mutations are additive for the metric trait, the decrease in fitness at homozygosity due to a mutant of frequency x is $(1 - 2h)sx(1 - x) + a^2x(1 - x)/4V_{s,r}$ (*cf.* Lynch and Walsh 1998, Chap. 10). Using Kimura's (1969) diffusion approximation of heterozygosity for $2N\bar{E}(\tilde{s}) \gg 1$, the inbreeding load measured by the effective number of lethal equivalents is $<(1 - 2h)\lambda/h + V_G/2V_{s,r}$ (*cf.* Charlesworth and Charlesworth 1999). For typical estimates of mutation and selection parameters (*i.e.*, $\lambda = 0.1$, $h = 0.1$, and $V_{s,r} = 20V_E$), the inbreeding load is thus ~0.81. As the effects of mutations are highly leptokurtic, the inbreeding load is likely to be smaller than this. For example, if mutational effects a and s follow reflected gamma (0.0847) and gamma (0.125) distributions, respectively, the inbreeding load is 0.52 in a population of size 10^5. These predictions are in the range of empirical data (Lynch and Walsh 1998, Chap. 10) and our model is thus robust to inbreeding depression. Another important test of the joint-effect model presented here is to compare observed and predicted changes in V_G with partial inbreeding. Our preliminary analysis shows that with the typical estimates of mutation and selection parameters assumed here, partial inbreeding leads to an increase in V_G for traits closely related to fitness and a decrease for others. Those results are in agreement with the empirical data (Garcia *et al.* 1994; Fernandez *et al.* 1995; Whitlock and Fowler 1999). The model could be further tested by predicting the pattern of response to multiple generations of artificial selection for quantitative traits in laboratory populations derived from natural populations, in particular the duration of response and the variability among replicate selection lines. Predictions could be compared to the results of the many such experiments that have been undertaken, particularly in Drosophila (Hill and Caballero 1992; Falconer and Mackay 1996).

Depending on the relation between the metric trait and fitness, the correlation between $|a|$ and s can be weak or strong. For a morphological trait, the correlation seems unlikely to be strong (and the respective marginal distributions of a and s are thus quite different), and its genetic variance can be well approximated by the prediction for an independent metric trait. For a fitness-related trait such as fecundity, the correlation can be strong (and the respective marginal distributions of a and s are similar to some extent), so its genetic variance is expected to be low because mutants with large effects are lost quickly from the population. This prediction is in agreement with empirical data (Houle *et al.* 1996). With a weak correlation such that some mutant genes have appreciable effects on the metric trait but small effects on fitness (Lyman *et al.* 1996), mutants with large effects on the trait can also have high frequencies even under strong apparent stabilizing selection. This is pre-

dicted to be the genetic basis of large genetic variance observed in the present model (Mackay 2001).

With the joint-effect model presented here, it is possible to explain the common phenomenon that multiple traits under strong apparent stabilizing selection have abundant variation (Falconer and Mackay 1996; Bürger 2000). In a study to investigate the nature of the pleiotropic effect (Zhang and Hill 2003), we show that the pleiotropic effect arising from purely multivariate stabilizing selection should generate a distribution with a much lower kurtosis than that of mutational effects on the metric traits. Although in principle infinitely many traits exist, these are correlated (Falconer and Mackay 1996) and could be classified into finite (perhaps small number of) groups according to their correlations. With high correlations within and low correlations between groups, the pleiotropic effect from multivariate stabilizing selection can be viewed as due to a few independent traits, so the kurtosis of this pleiotropic effect should not then be much smaller than that of mutational effects on the traits. On the other hand, such pleiotropic fitness effects of mutations, due to the nonlinear relationship between the direct action of the mutant on the metric traits and its pleiotropic effect on fitness, appear to be much more recessive than their direct effects on traits. If the effects due to nonstabilizing selection, which must be components of the true pleiotropic fitness effect, are leptokurtic or not predominant, then high genetic variances in quantitative traits can be maintained under fairly strong apparent stabilizing selection.

It was recognized that the shapes of the distributions of mutational effects are important in maintaining the genetic variance at MSB (Keightley and Hill 1990; Caballero and Keightley 1994; Zhang *et al.* 2002). Such distributions are hard to estimate accurately (*e.g.*, Mackay *et al.* 1992; Keightley 1994; Chavarrias *et al.* 2001), although the distribution of fitness effects among beneficial mutations has been predicted by Orr (2003), using extreme value theory. Hence, a variety of distributions of a and s, which have kurtoses roughly in agreement with available data (Mackay *et al.* 1992; Keightley 1994; Lyman *et al.* 1996; García-Dorado *et al.* 1999; Garcia-Dorado and Caballero 2000; Chavarrias *et al.* 2001), have been employed. To illustrate the robustness of the model, the extreme values of strength of real stabilizing selection, *i.e.*, $V_{r,s} = 20V_E$ (Turelli 1984; Endler 1986; Falconer and Mackay 1996), of the mutation rate, *i.e.*, $\lambda = 0.1$ and 0.01 for multicellular eukaryotes (Keightley and Eyre-Walker 1999; Lynch *et al.* 1999; García-Dorado *et al.* 2003), and of the average pleiotropic effect on fitness, *i.e.*, $\bar{s}_p = 0.1$ (Lynch *et al.* 1999; García-Dorado *et al.* 2003) have been used for numerical predictions from the model. Provided the kurtosis of the distribution of mutational effect on the trait is not $> \sim 10$ times that of the pleiotropic effect on fitness, even for such extreme situations, analyses presented here show that the joint-effect model of both continuously varying mutational effects and their dominance coefficients can satisfactorily explain the typical observed levels of V_G and $V_{s,t}$. This indicates that inclusion of more realistically variable dominance of mutations strengthens the previous joint-effect model (Zhang and Hill 2002) and lends further support to mutation-selection balance as a mechanism of the maintenance of the genetic variance in natural populations.

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APPENDIX

Suppose both the pleiotropic fitness effect (s) and effect on the metric trait (a) follow a gamma and a reflected square-root gamma distribution, respectively; *i.e.*, both a^2 and s follow gamma distributions with param-

eters (α_1, β_1) and (α_2, β_2), respectively. The distribution of a is given by $g_1(\alpha_1, \beta_1; a) = \alpha_1^{\beta_1}|a|^{2\beta_1-1}\exp(-\alpha_1 a^2)/\Gamma(\beta_1)(|a| < \infty)$, with $E(a) = 0$, $\varepsilon_a^2 = E(a^2) = \beta_1/\alpha_1$, $\mathrm{Var}(a) = \varepsilon_a^2$, and kurtosis $k_4(a) = (\beta_1 + 1)/\beta_1$; while s has mean $E(s_p) = \bar{s}_p = \beta_2/\alpha_2$ and $k_4(s) = (\beta_2 + 2)(\beta_2 + 3)/[\beta_2(\beta_2 + 1)]$. Making the transformation (a, s) to (a, v) where the ratio $v = (s/\bar{s}_p)/(a^2/\varepsilon_a^2)$ is a β random variable of the second kind (Moran 1968, p. 332) with a density function $(\varepsilon_a^2/\bar{s}_p)\int_0^\infty g_1(a)g_2(va^2s_p/\varepsilon_a^2)a^2da = (v\beta_2/\beta_1)^{\beta_2}\{[(1 + v\beta_2/\beta_1)^{\beta_1+\beta_2}]vB(\beta_1, \beta_2)\}^{-1}$, where $B(\beta_1, \beta_2)$ is the β function of parameters β_1 and β_2. Noting that $(\varepsilon_a^2/\bar{s}_p)\int_0^\infty g_1(a)g_2(va^2s_p/\varepsilon_a^2)a^4da = \varepsilon_a^2(v\beta_2/\beta_1)^{\beta_2}\{[(1 + v\beta_2/\beta_1)^{\beta_1+1+\beta_2}]vB(\beta_1 + 1, \beta_2)\}^{-1}$ and making the transformation $t = (v\beta_2/\beta_1)^{\beta_2}$, we have for infinite populations in which $2N\mathcal{E}(\hat{s}) \gg 1$ holds,

$$V_G = 4\lambda V_{sr}[\beta_2 B(\beta_1, \beta_2)]^{-1}\int_0^\infty [(1 + t^{1/\beta_2})^{\beta_1+\beta_2}(1 + \theta t^{1/\beta_2})]^{-1}dt,$$

$$m_4 = 2(2h')^2V_mV_{sr}[\beta_2 B(\beta_1 + 1, \beta_2)]^{-1}\int_0^\infty [(1 + t^{1/\beta_2})^{\beta_1+1+\beta_2}(1 + \theta t^{1/\beta_2})]^{-1}dt,$$

where $\theta \equiv (2h\bar{s}_p/\beta_2)/((2h')^2\bar{s}_t/\beta_1)$. Further assuming that $\beta_1 + \beta_2 = 1$,

$$V_G = 4\lambda V_{sr}(1 - \theta^{1-\beta_2})/(1 - \theta),$$

$$m_4 = 2(2h')^2V_mV_{sr}(1 - \beta_2 - (2 - \beta_2)\theta + \theta^{2-\beta_2})/[(1 - \beta_2)(1 - \theta)^2],$$

and

$$\mathrm{Cov}_P = (2h')^2V_m(\beta_2\theta + (1 - \beta_2)\theta^2 - \theta^{2-\beta_2})/[(1 - \beta_2)(1 - \theta)^2]$$

(*cf.* Zhang and Hill 2002).