THE SELECTIVE VALUE OF ALLELES UNDERLYING POLYGENIC TRAITS

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ABSTRACT

To define the genetic and ecological circumstances that are conducive to evolution via genetic drift at the allelic level, the selection coefficient for a constituent allele of arbitrary effect is derived for a polygenic character exposed to stabilizing selection. Under virtually all possible conditions, alleles within the class for which the absolute value of the average effect is $<10^{-2}$ phenotypic standard deviations are neutral with respect to each other. In addition, when the mean phenotype is at the optimum and the genetic variance is in selection-drift-mutation equilibrium, a considerable amount of neutral evolution is expected in the class of alleles with intermediate effects on the phenotype. These results help clarify how molecular evolution via genetic drift may occur at a locus despite intense selection and provide a potential mechanistic explanation for the neutral theory of molecular evolution.

THE resolution of many problems in evolutionary biology and population genetics requires accurate information on the intensity of selection operating on individual alleles. Nowhere is this more apparent than in the evaluation of the assumptions underlying the neutral theory of molecular evolution (KIMURA 1983a,b). Yet, the direct estimation of selection coefficients is not an easy task, particularly when the magnitude of fitness difference between alleles is on the order of 1% or less (LEWONTIN 1974). Under such circumstances, the statistical verification of the operation of selection on a single locus in a natural population requires enormous sample sizes gathered over a number of consecutive generations as well as ancillary information on effective population size and the magnitude of migration. From the perspective of the neutral theory, this is not a trivial matter since alleles with selection coefficients on the order of ± 0.001 can hardly be regarded as neutral for effective population sizes greater than ~ 500 . How then is it possible to verify when the conditional requirements of the neutral theory are likely to be fulfilled?

A promising approach to the analysis of selection at the gene level derives from recent attempts to express the selection coefficient of an allele as a function of properties revealed at the phenotypic level. Both MILKMAN (1978) and KIMURA and CROW (1978) have estimated the selection coefficient for an allele at a constituent locus of a polygenic character to be

$$s(g_i) \approx Sg_i/V_T \quad (1)$$

where S is the total selection differential on the character (the difference in the phenotypic mean before and after selection, each phenotype being weighted by its relative reproductive contribution to the next generation), and V_T is the phenotypic variance for the character. g_i is the average effect of allele i measured as a deviation of the average phenotype of an individual with allele i from the population mean ($\bar{z}$) such that under random mating

$$g_i = \sum_j p_j z_{ij} - \bar{z}$$

where p_j is the frequency of the j th allele and z_{ij} is the mean phenotype of an individual of genotype ij . For additive systems,

$$\begin{aligned} g_i &= \sum_j p_j (a_i + a_j + \bar{z} - 2\bar{a}) - \bar{z} \\ &= a_i - \bar{a} \end{aligned}$$

where a_i is the absolute contribution of the i allele to the phenotypic value and $\bar{a}$ is the mean genic effect of the locus. $s(g_i)$ is a measure of the selective advantage of allele i relative to the population mean such that

$$s(g_i) = \frac{W(g_i) - \bar{W}}{\bar{W}} \quad (2)$$

where under random mating

$$\begin{aligned} W(g_i) &= \sum_j p_j W(g_i, g_j), \\ \bar{W} &= \sum_i p_i \sum_j p_j W(g_i, g_j), \end{aligned}$$

with $W(g_i, g_j)$ being the mean fitness of a genotype with alleles i and j . When expressed in this form, the selection coefficient is directly related to the change in allele frequency by

$$\Delta p_i = p_i s(g_i).$$

The attractiveness of equation (1) lies in the fact that it is a function of three phenotypic properties (S , g_i and V_T) that are themselves functions of the environment and the genetic architecture of a population. Even though the sampling variances of these parameters may be prohibitively large for the direct attainment of highly accurate estimates of $s(g_i)$ without enormous sample sizes, mechanistic formulations such as (1) are of considerable theoretical interest since they may be used to explore the ecological and genetic circumstances that influence the relative sensitivity of alleles to the forces of selection and drift. Both KIMURA and CROW (1978) and MILKMAN (1982), for example, have interpreted (1) to imply the unconditional neutrality of alleles when $S = 0$ as when the mean phenotype is at the optimum. Were this to be true in an absolute sense, and if it is assumed that phenotypes in most populations are in fine tune with their local optima, equation (1) would provide a powerful ex-

planation for the approximate neutrality of individual genes despite the operation of stabilizing selection on phenotypes. Intuitively, however, under stabilizing selection, the relative fitness of individual alleles should be dependent on the deviation of their average effect from the optimum phenotype. Therefore, it becomes desirable to have a more exact expression for $s(g_i)$.

Whereas MILKMAN'S (1978) derivation of equation (1) was essentially a graphical approximation, KIMURA and CROW (1978) developed a general technique based on Taylor expansion which could be utilized to derive a more precise expression for $s(g_i)$ (cf. KIMURA 1981). The KIMURA and CROW (1978) method is extremely useful because it makes no assumptions about the shapes of the phenotype distribution or the fitness function. Nevertheless, the arbitrary degree of approximation that is necessary in the application of the KIMURA and CROW (1978) technique can be avoided for characters that are normally distributed on some scale of measurement. The latter condition can be fulfilled for most continuously distributed characters (WRIGHT 1968; FALCONER 1981), most often because of the superimposition of multiple environmental effects on the genetic background. Approximate normality of genotypic values is also expected when the forces of selection and mutation are weak relative to recombination and when the effective population size and number of loci are large (LANDE 1976; FLEMING 1979; CHAKRABORTY and NEI 1982). TURELLI (1984) has recently published a critical analysis of these issues.

SELECTION ON CONSTITUENT ALLELES OF CHARACTERS UNDER STABILIZING SELECTION

The following analyses assume that the criteria for normality of phenotypes and genotypes are met. Implicit in this assumption is the existence of global linkage equilibrium between loci and an effectively infinite number of allelic effects per locus (CROW and KIMURA 1965). For a character with an additive genetic basis, the total phenotypic variance (V_T) may be partitioned into two components: V_G , the additive genetic variance due to all constituent loci, and V_e , the environmental variance. For the more restricted group of individuals with an allele of effect g_i at the i th locus, the phenotypic variance, V'_T , is $[1 - (\alpha_i/2)]V_G + V_e$, where α_i is the proportion of the total additive genetic variance attributable to the i th locus. (From here on, I will drop the subscript i since it is implicit that a single locus is under consideration.)

Provided that the character has been measured on or transformed to a scale that yields a normal distribution with $\bar{z} = 0$, the expected phenotypic distribution for individuals with an allele of average effect g is

$$p(z|g) = [2\pi V'_T]^{-1/2} \cdot \exp \left\{ -\frac{(z - g)^2}{2V'_T} \right\}.$$

The mean fitness of individuals with allele g is

$$W(g) = \int_{-\infty}^{+\infty} p(z|g) \cdot W(z) \cdot dz \quad (3)$$

where, under stabilizing gaussian selection,

$$W(z) = [2\pi V_w]^{-1/2} \cdot \exp \left\{ -\frac{(z - \theta)^2}{2V_w} \right\}$$

with θ being the optimum phenotype and V_w being a measure of the width of the fitness function inversely related to the intensity of selection. Since equation (3) is a convolution of two normal distributions, its solution must also be normal with variance $(V_T + V_w)$ and optimum θ ,

$$W(g) = [2\pi(V_T + V_w)]^{-1/2} \cdot \exp \left\{ -\frac{(g - \theta)^2}{2(V_T + V_w)} \right\}.$$

The mean population fitness, $\bar{W}$, can be derived in a similar manner. Since the environmental effects are assumed to be independent of g and distributed normally with mean zero, then initially $\bar{z} = 0$. The phenotype distribution for the entire population is, therefore,

$$p(z) = [2\pi V_T]^{-1/2} \cdot \exp \left\{ -\frac{z^2}{2V_T} \right\}$$

By substitution,

$$\begin{aligned} \bar{W} &= \int_{-\infty}^{+\infty} p(z) \cdot W(z) \cdot dz \\ &= [2\pi(V_T + V_w)]^{-1/2} \cdot \exp \left\{ -\frac{\theta^2}{2(V_T + V_w)} \right\}. \end{aligned}$$

Finally, the selection coefficient for allele g is found by substituting $W(g)$ and $\bar{W}$ into equation (2)

$$s(g) = \left\{ \frac{V_T + V_w}{V_T + V_w} \right\}^{1/2} \cdot \exp \left\{ -\frac{1}{2} \left[\frac{g(g - 2\theta)(V_T + V_w) + V_g \theta^2}{(V_T + V_w)(V_T + V_w)} \right] \right\} - 1. \quad (4)$$

We may now evaluate the intensity of selection operating on individual alleles for the special case in which the population mean phenotype has been stabilized at the optimum; *i.e.* $\theta = 0$. Under these circumstances, equation (4) simplifies to

$$s(g) = \left\{ \frac{V_T + V_w}{V_T + V_w} \right\}^{1/2} \cdot \exp \left\{ -\frac{g^2}{2(V_T + V_w)} \right\} - 1. \quad (5)$$

As expected, when the population mean is at the optimum, there is some selection against alleles whose average effects deviate from the optimum ($g \neq 0$). The intensity of selection against a deviant allele depends directly upon the ratio of its squared effect relative to the sum of the phenotypic and fitness function variances. As the phenotypic variance increases, either for genetic or environmental reasons, an individual allele will be found in an increasing range of phenotypic backgrounds and, hence, will be less subject to selective discrimination (JAENIKE 1982).

The first bracketed term in equations (4) and (5) clarifies another important determinant of the selection coefficient of an allele. Since this quantity increases with α , it is clear that the intensity of selection operating on an allele is directly dependent on the relative contribution that its locus makes to the total genetic variance. In general then, the intensity of selection on constituent alleles is likely to decline with an increase in the number of segregating factors underlying a polygenic trait as suggested earlier by CROW and KIMURA (1970).

Equation (5) also provides some insight into the qualitative nature of selectively neutral alleles under stabilizing phenotypic selection. Since the first bracketed term is necessarily a constant greater than 1, while the exponential term decreases from 1 with increasing g^2 , $s(g)$ must be positive and at a maximum when $g = 0$ and thereafter must decrease monotonically with increasing g^2 . Thus, under stabilizing phenotypic selection, alleles with minimal average effects are positively selected, whereas those that cause relatively large deviations from the population mean are selected against. This frequency-dependent property of genic selection results in a class of alleles with intermediate effects being rendered closest to neutrality. Setting $s(g)$ equal to zero and solving equation (5) reveals that, for a given genetic environment, the frequency of an allele with average effect

$$g^* = \pm \left\{ -2(V_T + V_w) \cdot \ln \left[\left(\frac{V_T + V_w}{V'_T + V_w} \right)^{-1/2} \right] \right\}^{1/2}$$

would be unaltered by selection despite the fact that it encoded for suboptimal phenotypes. Provided that $\theta = 0$ and that the genetic variance is in its steady state (below), then a considerable amount of random evolution via drift may occur in the class of alleles with average effects near g^* .

Figure 1 provides a more general picture of the circumstances required to render an allele effectively neutral under stabilizing selection. Each of the panels in this figure contains the solutions to equation (5) for specific values of α and $h^2 = V_G/V_T$ for four values of V_w . The range of α , h^2 and V_w examined in this figure should cover almost all conceivable circumstances in natural populations. For clarity V_w is represented as the percent-selective mortality which under gaussian selection is equal to

$$100 \left\{ 1 - \left[\frac{V_w}{V_T + V_w} \right]^{1/2} \right\} \quad (6)$$

(LATTER 1970; LYNCH and GABRIEL 1983). The general criterion for effective neutrality, $|s(g)| < 1/4N_e$, is represented for $N_e = 10^3$ and 10^4 by dashed and dotted lines, respectively. Circumstances that result in $s(g)$ outside of these boundaries are incompatible with effective neutrality. Since $s(g)$ calculated by equation (1) is zero whenever $\theta = 0$, Figure 1 also provides some insight into the magnitude of error introduced by using this approximation.

Provided that $|g|/\sqrt{V_T} < 0.01$, the selective mortality is $<10\%$, and $\alpha \leq 0.001$, an allele will virtually always be effectively neutral even for very large effective population sizes ($N_e > 10^4$) and even when the environment has very

FIGURE 1.—The selection coefficient, $s(g)$, as a function of the standardized average effect of an allele, $|g|/\sqrt{V_T}$, under the assumption that the population mean phenotype is at the optimum. The function $s(g)$ is plotted for various values of α and h^2 , and the labels on the individual curves denote the percent-selective mortality. The dotted and dashed lines are $|s(g)| = (1/4N_e)$ for $N_e = 10^4$ and 10^3 , respectively; points lying inside these boundaries imply effective neutrality.

little influence on the expression of the character (high h^2). Because a methodology for the precise determination of gene number does not exist, the general validity of the condition $\alpha \leq 0.001$ (which implies $\sim 10^3$ loci underlying selected traits) is difficult to assess. However, minimum estimates for the number of loci for quantitative characters generally range from ~ 10 to 200 (WRIGHT 1968; DUDLEY 1977; COMSTOCK and ENFIELD 1981; LANDE 1981a). Moreover, uncertainty as to the value of α does not greatly obscure the message of Figure 1. For example, even when $\alpha \gg 0.001$, members of the class of alleles underlying characters for which the selective mortality is $< 0.1\%$ are virtually always effectively neutral with respect to each other provided that $|g|/\sqrt{V_T} < 0.1$. For selective mortalities $> 0.1\%$ an increase in α results in a significant increase in the selection intensity on alleles, but a large region of relatively constant $s(g)$ still remains for alleles with small average effects. Finally, Figure 1 illustrates that, although the selection coefficient increases in magnitude with increasing h^2 , the effect is negligible except when the selective mortality $\gg 1\%$ and/or $\alpha > 0.1$.

Thus, the analysis in Figure 1 allows a general statement about the neutral theory. Even though alleles of the class $|g|/\sqrt{V_T} < 0.01$ may be strongly favored under many circumstances, the members of this group always have

virtually identical selection coefficients and, hence, will behave neutrally with respect to each other. Therefore, under stabilizing selection, the allelic pool can be partitioned into a positively selected group of alleles with relatively minor average effects and among which considerable drift can be expected and a negatively selected group of alleles with larger effects and a low likelihood of being influenced by drift. Since the exponential term in equation (4) approaches a constant asymptotically as $|g|/\sqrt{V_T}$ becomes small, this statement applies to some degree even if the population mean is not at the optimum. These results help clarify how considerable drift may occur at a locus despite its exposure to intense selection and support the neutral theory of molecular evolution.

THE EFFECT OF SELECTION ON THE EVOLUTIONARY DYNAMICS OF CONSTITUENT LOCI

Under the conditions defined, $\bar{g} = \sum p_i(a_i - \bar{a})$ and the allelic distribution for the locus is

$$p(g) = [2\pi V_g]^{-1/2} \cdot \exp \left\{ -\frac{g^2}{2V_g} \right\} \quad (7)$$

where $V_g = \alpha V_G/2$ is one-half of the genotypic variance at the locus. The operation of phenotypic selection will cause a change in this distribution defined by

$$p[g(t+1)] = p[g(t)] \cdot \{1 + s[g(t)]\}.$$

Substituting (4) and (7), the new allelic distribution prior to the input of mutations is found to be

$$p[g(t+1)] = \left\{ \frac{2\pi V_g(t)[V_T'(t) + V_w]}{V_T(t) + V_w} \right\}^{-1/2} \cdot \exp \left\{ -1/2 \left[\frac{(g(t+1) - \{V_g(t)\theta/[V_T(t) + V_w]\})^2}{V_g(t)[V_T'(t) + V_w]/[V_T(t) + V_w]} \right] \right\}.$$

This is a normal distribution with mean $V_g(t)\theta/[V_T(t) + V_w]$ and variance $V_g(t)[V_T'(t) + V_w]/[V_T(t) + V_w]$. Thus, selection toward a new optimum phenotype θ units from the original mean will cause an expected response in average effect (measured relative to the original mean) of genotypes at a constituent locus of

$$\Delta 2\bar{g}(t) = \frac{2\theta V_g(t)}{V_T(t) + V_w}, \quad (8)$$

and a change in genotypic variance of

$$[\Delta 2V_g(t)]_s = \frac{2V_g(t)[V_T'(t) + V_w]}{V_T(t) + V_w} - 2V_g(t) \quad (9)$$

where the subscript s denotes change due to selection.

By further accounting for drift and mutation, the expected dynamics of genetic variance at a constituent locus underlying a character exposed to stabilizing selection are defined by

$$2V_g(t+1) = 2V_g(t) \left\{ \frac{V'_T(t) + V_w}{V_T(t) + V_w} \right\} \cdot \left\{ 1 - \frac{1}{2N_e} \right\} + V_m \quad (10)$$

where N_e is the effective population size and V_m is the mutational rate of input of genetic variance for the locus. As noted earlier by LANDE (1976) and LYNCH and GABRIEL (1983) for phenotypes, provided that conditions for normality are maintained, the dynamics of genetic variance at the constituent loci are independent of the distance of the population mean phenotype from the optimum. For constant α , V_w , V_m and N_e and $2[N_e + (1/\alpha)] \gg 1$, the expected equilibrium level of genetic variance at a locus will be

$$2\hat{V}_g = \frac{\{2N_e V_m - \alpha V^*\} + \sqrt{\{\alpha V^* - 2N_e V_m\}^2 + 8\alpha N_e V^* V_m (\alpha N_e + 1)}}{2(\alpha N_e + 1)} \quad (11)$$

where $V^* = V_e + V_w$. When the effective population size is assumed to be infinite, the expression reduces to α times the total expected equilibrium level of genetic variance ($\hat{V}_G$) as derived by LANDE (1976; equation 25).

Equation (11) will be most accurate when the intensity of selection is low and the average effect of new mutations is small. FLEMING (1979) and TURELLI (1984) may be consulted for alternative expressions when these conditions are violated. In addition, for small population sizes, the loss of genetic variance by drift and the input of new variance via mutation may vary considerably between generations because of the stochastic nature of the sampling process (LATTER 1970, 1972). This will cause the distribution of g to deviate from normality and will result in fluctuations of actual levels of V_g around the expected equilibrium (CHAKRABORTY and NEI 1982). Therefore, equations (7)–(11) should only be taken as approximations of the expected properties of constituent loci.

DISCUSSION

The theory developed provides a quantitative statement on the genetic and ecological circumstances that are conducive to evolution at the molecular level via random genetic drift. The neutral theory is strongly supported for the class of alleles for which $|g|/\sqrt{V_T} < 0.01$. Regardless of the intensity of selection operating on this class of alleles, the relative frequencies of its constituent members will be primarily governed by random genetic drift since they are selectively equivalent with respect to each other. Thus, if only a small proportion of mutations at a locus with effects >0.01 are fixed due to their favorable effects on the phenotype, then the majority of observed allelic substitutions will be due to drift within the class of alleles with effects <0.01 . These results help explain the apparent independence of evolutionary rates at the molecular and phenotypic level (WILSON, CARLSON and WHITE 1977).

This analysis also indicates that, under all circumstances, there will be a second intermediate class of alleles with $|g|/\sqrt{V_T} > 0.01$ which is effectively neutral [$|s(g)| < 1/4N_e$] with respect to the entire allelic population. Provided that the genetic variance at the locus is approximately in selection-drift-mutation equilibrium and that the optimum phenotype remains approximately constant, then considerable evolution via genetic drift can be anticipated in this second class of alleles despite the fact that they cause a deviation of the phenotype from the optimum.

A third source of neutral molecular evolution, which has previously attracted the most attention but is not explicitly addressed, is independent of g and results from changes in molecular state that do not influence g . LANDE (1976) has pointed out another important property of polygenic systems that may be highly conducive to random genetic drift even in very large populations. Under stabilizing selection, the only constraint on the mean genic values of different loci is that the grand mean over all n loci is equal to the optimum; *i.e.*,

$$2 \sum_{k=1}^n \bar{a}_k = 0.$$

Thus, for polygenic characters, random genetic drift might cause considerable divergence between populations in mean genic values of constituent loci with little or no change in the phenotypic mean.

Although the evidence for molecular evolution via genetic drift is now quite strong (KIMURA 1983b), there are a number of unanswered questions. It is well known that different genes evolve at different rates, but with few exceptions, the rate of allelic substitution at a given locus appears to be approximately constant on an absolute time scale (WILSON, CARLSON and WHITE 1977). This discovery has led to the widespread use of molecular clocks as phylogenetic tools (THORPE 1982). There are two ways to account for the absolute time dependency of molecular evolution. First, for purely neutral mutations [$s(g) = 0$], the expected rate of allelic substitution is equal to the mutation rate and independent of effective population size (KIMURA 1968). Thus, if the majority of observed allelic substitutions were absolutely neutral, the constancy of the rate of molecular evolution would be accounted for if the mutation rate to such alleles were constant on an absolute time scale. Alternatively, if the majority of allelic substitutions are not neutral in an absolute sense, constancy of the molecular clock might still arise if species with relatively low mutation rates (on an absolute time scale) and/or relatively large selection coefficients for mutant alleles tended to have relatively low effective population sizes. An inverse relation between these factors of the appropriate magnitude might result in a constant substitution rate for effectively neutral mutations on an absolute time scale (KIMURA 1983a).

Existing data tend to support the first hypothesis. Although a mechanistic explanation is not yet available, it appears that the incidence of mutations is more a function of absolute time than number of generations passed. Comparative data for single-locus mutation rates (NOVICK and SZILARD 1950;

DRAKE 1970; HARTL and DYKHUIZEN 1979) are supportive of this hypothesis. Moreover, a recent analysis of phenotypic data from *Daphnia*, *Drosophila*, *Tribolium*, *Mus*, *Zea* and *Oryza* strongly suggests that the rate of input of genetic variance via polygenic mutation is a positive function of generation time with expected value $10^{-4} V_e \times \text{generation time in days}$. These observations are consistent with an approximately constant rate of input of mutations into the effectively neutral class of alleles per unit time and, providing V_w is approximately constant for different species, would explain the absolute time dependence of the rate of allelic substitutions at a locus. Arguments exist for the approximate constancy of V_w (VAN VALEN 1973), although they lack empirical verification. Thus, although it is not clear whether the criteria are met, the analysis has provided suggestions as to the types of studies that need to be performed to uncover the genetic and ecological basis for the molecular clock.

In my analysis I have relied on the use of a gaussian fitness function. For natural populations there seems to be little justification for invoking major deviations from this form of the fitness function. The gaussian function has the useful property, $0 < W(g) < \infty$, which is not shared by many linear, exponential and quadratic functions. Moreover, the few attempts to directly measure the relation between fitness and phenotype have generally found intermediate optima (RENDEL 1943; LACK 1966; VAN VALEN and MELLIN 1967; CHARNOV 1982; WELS, PRICE and LYNCH 1983). The general observation that the mean phenotype of artificially selected populations regresses toward the original mean when selection is relaxed (FALCONER 1981) provides further evidence for the ubiquity of stabilizing selection. Even sexual selection, which is often viewed as an extreme form of directional selection, can be interpreted through the use of gaussian function (LANDE 1981b).

In cases in which the phenotype distribution and the fitness function are not normal on the same scale of measurement, the KIMURA and CROW (1978) technique may be relied upon to derive $s(g)$. This will provide an adequate approximation provided that care is taken to truncate the Taylor expansion at a point that will not be a significant influence at the desired level of resolution. It should be noted, however, that an exact solution of (3) is often possible even when the fitness function is not normally distributed. LATTE (1965), for example, has performed such a derivation for the truncation selection function. His paper may be consulted to determine the adequacy of equation (1) for artificial selection programs.

The practical value of equations such as (4) and (5) lies principally in the insight they offer into the genetic and ecological circumstances that determine the relative sensitivity of an allele to the forces of drift and selection. Given that information on the parameters of these equations is available for actual situations, they might also be useful for generating preliminary hypotheses on selection coefficients at specific loci. It must be noted, however, that estimates of $s(g)$ based on the solution of (4) may have very high sampling variances unless sample sizes are extremely large. An approximate estimate for the sampling variance of $s(g)$ can be derived by the delta technique (BULMER 1980). Ignoring higher order terms, from (4),

$$\begin{aligned}\text{Var}[s(g)] \approx & \left[\frac{\partial s(g)}{\partial V_T} \right]^2 \text{Var}(V_T) + \left[\frac{\partial s(g)}{\partial V'_T} \right]^2 \text{Var}(V'_T) \\ & + \left[\frac{\partial s(g)}{\partial V_w} \right]^2 \text{Var}(V_w) + \left[\frac{\partial s(g)}{\partial g} \right]^2 \text{Var}(g) \\ & + \left[\frac{\partial s(g)}{\partial \theta} \right]^2 \text{Var}(\theta) + \left[\frac{\partial s(g)}{\partial V_g} \right]^2 \text{Var}(V_g).\end{aligned}$$

It is not necessary to evaluate this entire expression to illustrate the statistical difficulties that are likely to arise in any direct attempt to test the hypothesis of selective neutrality. Noting that for small α , $V'_T \approx V_T$, and that for a normally distributed trait, $\text{Var}(V_T) = 2V_T^2/N$, where N is the sample size for the phenotype distribution, the sum of the first two terms in the equation is found to be approximately

$$\left\{ \frac{[s(g) + 1]V_T}{V_T + V_w} \right\}^2 \cdot \frac{1}{N}.$$

The square root of this quantity provides a minimum estimate of the standard error of $s(g)$, since the variance of all terms other than V_T and V'_T has been ignored. For $s(g) < 0.1$, this quantity is approximately $[V_T/(V_T + V_w)]/N^{1/2}$. Thus, for a case of moderate selection [5% selective mortality when $V_T/(V_T + V_w) = 0.1$; from (6)], the minimum standard errors of $s(g)$ when $N = 10^2$, 10^3 and 10^4 are 0.010, 0.003, and 0.001, respectively. Parallel estimates for a case of strong selection [29% selective mortality when $V_T/(V_T + V_w) = 0.5$] are 0.050, 0.016 and 0.005. In all of these cases, the minimum standard error of $s(g)$ is $>1/N$ which will in general be $\gg 1/4N_e$. Thus, a direct evaluation of $s(g)$ by equations such as (1), (4) and (5) will provide evidence for the non-neutrality of a polygene only under extreme circumstances and is unlikely to ever confirm the existence of selective neutrality of genes in natural populations.

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