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THE RESPONSE TO SELECTION ON MAJOR AND MINOR MUTATIONS AFFECTING A METRICAL TRAIT

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SUMMARY

The joint evolution of major and minor mutations influencing a quantitative character is modelled in a large population. Empirical data on natural and domesticated populations, and analysis of the models, suggests that strong selection sustained over several generations is usually required for adaptive evolution by a major mutation, in order to overcome deleterious pleiotropic effects generally associated with major mutations. This helps to explain why adaptive evolution by major mutations occurs much more frequently in domesticated and artificially disturbed populations than in natural ones.

1. INTRODUCTION

The genetic basis of major phenotypic changes is central to understanding mechanisms of evolution in natural and artificial populations. Recently, several authors have speculated that large phenotypic changes in natural populations may occur by the evolution of a single genetic mutation or chromosomal rearrangement with major effects (Wilson *et al.*, 1975; Bush *et al.*, 1977; Stanley, 1979; Gould, 1980). There is no question that a wide variety of mutations with major effects do occur spontaneously (Dobzhansky, 1970 Chapter 3; Lindsley and Grell, 1968; King, 1975) but there is at present relatively little evidence that they serve as the basis for adaptive evolution in natural populations. As will be shown below, adaptive evolution by mutations with major effects occurs most often in domesticated or artificially disturbed populations.

For the great majority of characters in which genetic mutations of large effect occur, mutations of small effect arise far more frequently (Muller, 1949 p. 432; Gregory, 1965). In higher organisms, typical rates of spontaneous mutation for single genes with major effect are on the order of 10^{-5} to 10^{-7} per gamete per generation (Schlager and Dickie, 1967; Dobzhansky, 1970 Chapter 3). In contrast, the total spontaneous rate for minor mutations at all loci influencing a given quantitative character may often be on the order of 10^{-2} per gamete per generation (Sprague *et al.*, 1960; Russell *et al.*, 1963; Hoi-Sen, 1972; Mukai *et al.*, 1972). Thus there is usually no reason to suppose that a major mutation is necessary to produce a given phenotype. For example, in genetic assimilation experiments the phenotype produced by a major mutation at the *bithorax* locus in *Drosophila* can be built up by selection of polygenic changes (Waddington, 1956; see also Bateman, 1959*a*, *b*).

Mutations of large effect are almost always deleterious, either due to their main effect or to pleiotropic effects on other characters (Wright, 1977

p. 463; Grüneberg, 1963; Lindsley and Grell, 1968). Fisher (1930, 1958 pp. 41–44) reasoned that in a population evolving toward an optimum phenotype, which usually requires the mutual adjustment of many characters, the probability that a random (undirected) mutation will improve adaptation decreases rapidly with increasing magnitude of its effect, being nearly half for mutations of small effect and quite low for mutations of large effect (see also Haldane, 1932 pp. 174–176). The high spontaneous rate of minor mutations, in addition to their much greater probability of improving adaptation compared with major mutations, explains why evolution in natural populations usually proceeds in the classical Darwinian mode, by a series of small steps. Numerous studies of natural populations have demonstrated that phenotypic differences between individuals within populations, as well as differences between populations, races, and species are generally influenced by multiple genetic factors with relatively small effects (Wright, 1968 Chapter 15; Falconer, 1981 Chapter 12; Lande, 1981; Coyne, 1983).

There are, however, some natural populations in which important adaptive changes have evolved from a mutation in a single gene. Best known is the balanced polymorphism for sickle cell anemia in humans; in regions with a high incidence of malaria, the mutant heterozygote is more fit than the normal homozygote, whereas the mutant homozygote is effectively lethal (Cavalli-Sforza and Bodmer, 1971 Chapter 4). Color polymorphisms are frequently influenced by major genes. Melanism in moths serves as camouflage against bird predation in industrial regions polluted with soot, and has often evolved from a single dominant mutation, and occasionally from a recessive one, although the degree of dominance is subject to genetic modification (Ford, 1975 Chapter 14). In butterflies which mimic a species unpalatable to bird predators, major changes in color pattern and alterations in wing shape appear to have started with a major mutation producing a crude resemblance to the model species, which was later improved by numerous minor genetic modifiers (Charlesworth and Charlesworth, 1975; Turner, 1977, 1981).

Examples of major adaptive changes conferred by a single gene are found most frequently in domesticated or artificially controlled populations, in the evolution of resistance to pesticides (Crow, 1957; Georghiou, 1972), or resistance to diseases and herbivores in crop plants (Nelson, 1977; Maxwell and Jennings, 1980). Detoxification of a specific chemical poison may be accomplished by a specific enzyme, such as the dehydrochlorinase of house flies which confers a high level of resistance to DDT. But there are usually multiple behavioral, physiological and biochemical mechanisms by which pest populations can evolve genetic resistance to particular control procedures, so that resistance even to specific chemicals is often polygenic (Crow, 1957; Georghiou, 1972).

Pure stands of crop plants, and domesticated animal populations, provide an artificial opportunity for outbreaks of pests and diseases that cause tremendous mortality and strong selection for resistance sustained over several generations. Such severe epidemics are probably uncharacteristic of most natural, coevolved systems, as illustrated by the history of myxomatosis in Australia. In an attempt to control the introduced rabbit population in Australia, a myxoma virus introduced from an African rabbit population was initially quite effective in reducing the Australian

rabbit population, but within a few years coevolution of the rabbits and the virus rendered the latter an ineffective control agent (Fenner and Ratcliffe, 1965).

Different populations or species sometimes respond differently to similar selection pressures, as shown by the following examples. Resistance to the poison Warfarin in rats is due to the heterozygous effect of a recessive lethal gene, whereas in mice Warfarin resistance is polygenic (Ford, 1975 pp. 378–379). Industrial melanism in the moth *Gonodontis bidentata* is produced by a single dominant gene in most populations, but is polygenic in Birmingham (Ford, 1975 Chapter 14). Resistance by wheat plants to wheat rust fungi has long been thought to be conferred by a single gene, but polygenic inheritance has been reported (Knott, 1982). In laboratory experiments with *Drosophila*, Crow (1957) found that larval resistance to DDT is monogenic, but that adult resistance is polygenic. Resistance by a crop plant to insect damage may range from monogenic to polygenic in different populations, as in corn populations infested with the European corn borer (Gallun and Khush, 1980).

A common feature of situations where important adaptation involved a single gene of major effect, especially in the artificial control of pest populations, is that selection for the phenotypic change was rather strong. Although the preceding examples indicate that strong selection may be necessary for the establishment of a major mutation, it is certainly not sufficient. It is not surprising that strong selection is often required to overcome the deleterious pleiotropic effects that are usually associated with mutations of large effect; but even under strong selection the initial frequency of a major mutation may be so low that selection cannot act efficiently on it, and a new adaptive phenotype may evolve more rapidly by polygenic changes.

In order to clarify the conditions which determine the genetic basis of large-scale evolutionary changes, the following models have been developed for a character influenced both by a single gene or chromosomal rearrangement of large effect, and by quantitative (polygenic) variation. Different forms of selection as well as different genetic systems are considered. Conditions are obtained for the fixation or adaptive polymorphism of a major mutation.

2. Selection on major and minor mutations

A simple model will be derived which describes the evolution of a character influenced by an autosomal locus, or chromosomal rearrangement, of major effect and by multiple loci of small effect which constitute the "genetic background" of the major locus. Heritable background variation is assumed to be maintained in a constant amount by polygenic mutation and recombination (Lande, 1975). This plus independent environmental effects combine to produce quantitative variation which is normally distributed around each genotype at the major locus.

Mating in the population is postulated to be random with respect to the character. If the major locus is unlinked or loosely linked to the genetic background, and selection is not very strong, the major locus will be approximately in linkage equilibrium (random combination) with the genetic background (Wright, 1969 Chapters 4, 5). Allelic dominance is

permitted, particularly at the major locus, but all genetic effects between loci are assumed to be additive. These assumptions entail that in any generation before selection the distribution of quantitative variation is the same around each genotype at the major locus, and the magnitude of effect of the major locus does not depend on the genetic background.

The phenotypic distribution of the character in any generation prior to selection is determined by two variables: the frequency of the major mutant allele, q, and the average effect of the polygenic background, $\bar{z}$, as follows.

Major locus genotype	AA	AA'	$A'A'$
Frequency	$(1-q)^2$	$2q(1-q)$	q^2
Mean phenotype	$\bar{z}$	$\bar{z}+\alpha_1$	$\bar{z}+\alpha_2$
Background variance	σ^2	σ^2	σ^2
Background heritability	h^2	h^2	h^2
Mean fitness	$\bar{w}_0$	$(1-s_1)\bar{w}_1$	$(1-s_2)\bar{w}_2$

α_1 and α_2 are the effects of the mutant heterozygote and homozygote on the character, respectively, and s_1 and s_2 are their selective disadvantages produced by pleiotropic effects on other characters. The background has total phenotypic variance σ^2, and the proportion of this due to the additive effects of all minor genes is its heritability h^2. This model could also describe approximately the evolution of most types of chromosomal rearrangements, which, through breakpoint or position effects or by suppressing recombination of genes near the breakpoints, are associated with a major effect on a quantitative character.

The phenotypic distribution for each of the genotypes at the major locus is

$$p_i(z)=\frac{1}{\sqrt{2\pi\sigma^2}}\exp\{-\tfrac{1}{2}(z-\bar{z}-\alpha_i)^2/\sigma^2\} \quad \text{for } i=0,1,2. \tag{1}$$

Selection on the character according to the fitness function $w(z)$ creates the components of the mean fitnesses for the major locus genotypes,

$$\bar{w}_i=\int p_i(z)w(z)\,dz \quad \text{for } i=0,1,2. \tag{2}$$

The mean fitness in the entire population is

$$\bar{w}=(1-q)^2\bar{w}_0+2q(1-q)(1-s_1)\bar{w}_1+q^2(1-s_2)\bar{w}_2. \tag{3}$$

The joint evolution of a major mutation and polygenic variation in response to selection is then described by a pair of equations for the change in the frequency of the major mutant allele and the change in average value of the polygenic background during one generation,

$$\Delta q=\frac{q(1-q)}{2\bar{w}}\frac{\partial\bar{w}}{\partial q} \tag{4a}$$

$$\Delta\bar{z}=\frac{h^2\sigma^2}{\bar{w}}\frac{\partial\bar{w}}{\partial\bar{z}} \tag{4b}$$

where

$$\frac{\partial \bar{w}}{\partial q} = 2[-(1-q)\bar{w}_0 + (1-2q)(1-s_1)\bar{w}_1 + q(1-s_2)\bar{w}_2]$$

$$\frac{\partial \bar{w}}{\partial \bar{z}} = (1-q)^2 \frac{\partial \bar{w}_0}{\partial \bar{z}} + 2q(1-q)(1-s_1)\frac{\partial \bar{w}_1}{\partial \bar{z}} + q^2(1-s_2)\frac{\partial \bar{w}_2}{\partial \bar{z}}.$$

The first equation (4a) is a well known formula of Wright (1969 Chapter 2). The second (4b) follows upon noting from (1) and (2) that

$$\sigma^2 \frac{\partial \bar{w}_i}{\partial \bar{z}} = \bar{w}_i \left[\bar{w}_i^{-1} \int z p_i(z) w(z)\, dz - \bar{z} - \alpha_i \right] \quad \text{for } i = 0, 1, 2 \tag{5}$$

where the term in brackets is the *selection differential* on quantitative variation around a particular genotype at the major locus, *i.e.*, the difference in mean phenotype of selected and unselected individuals within a generation (before reproduction). Equation (4b) therefore states that the evolutionary response in the mean of quantitative variation is equal to its heritability times the weighted average selection differential on it, which is a standard result of quantitative genetics (Falconer, 1981).

Provided that the fitness function acting on the character, $w(z)$, and the selection coefficients on the pleiotropic effects of the major mutant, s_1 and s_2, do not change with time, under weak selection the change in the mean fitness in the population can be approximated using (4a) and (4b) as

$$\begin{aligned} \Delta \bar{w} &\simeq \frac{\partial \bar{w}}{\partial q} \Delta q + \frac{\partial \bar{w}}{\partial \bar{z}} \Delta \bar{z} \\ &= \frac{q(1-q)}{2\bar{w}} \left(\frac{\partial \bar{w}}{\partial q} \right)^2 + \frac{h^2 \sigma^2}{\bar{w}} \left(\frac{\partial \bar{w}}{\partial \bar{z}} \right)^2 \geqq 0. \end{aligned} \tag{6}$$

The joint evolution of the major and minor genes continually increases the mean fitness in the population until an equilibrium is reached. Thus when selection is not very strong the population can be represented as a point evolving uphill on a surface of $\bar{w}$ as a function of q and $\bar{z}$. A stable equilibrium always occurs at a local maximum of $\bar{w}$. This model combines the adaptive topography of Wright (1969) for gene frequencies, and that of Lande (1976) for the mean value of quantitative variation, into a single selective surface.

We now examine various patterns of selection which might bring about the fixation or polymorphism of a mutation with major effect in the presence of small polygenic variations.

3. Conditions for fixation of a major mutation

(i) *Two or more adaptive peaks*

A mutation of major effect could allow a population to cross a valley between two adaptive peaks that could not be crossed by selection on small variations around a locally optimum phenotype. Petry (1982) has analyzed such a model in which a major mutation changes the fitness surface acting on a quantitative trait. However, in terms of the generalized adaptive

topography described above, the joint selection of major and minor mutations increases the net mean fitness, and the population always evolves uphill. Examples where a major mutation has crossed a valley between adaptive zones occur in the evolution of mimicry in butterflies, where in some species the most fit individuals are either cryptic or closely resemble a model species that is distasteful to birds; intermediate individuals that are neither cryptic nor good mimics of a distasteful model are more likely to be eaten. In a butterfly species that is camouflaged against predators, but not perfectly so, mutations of small effect which decrease crypsis are selected against, but there is a potential selective advantage for mutations with a sufficiently large effect to produce a passable similarity to a distasteful model. The selective advantage of mimicry may be frequency-dependent, leading to adaptive polymorphism (Ford, 1975; Charlesworth and Charlesworth, 1975; Turner, 1977, 1981).

Even if a major mutation does enter a new adaptive zone, in order for it to increase in frequency, it is still necessary for the selective advantage of its major effect to outweigh the disadvantage of its deleterious pleiotropic effects. If the major mutation reaches high frequency in the population, there may then be selection for further genetic changes to increase the adaptive value of the new phenotype by modifying the main effect or the pleiotropic side-effects of the major mutant (Wright, 1977 p. 463).

(ii) *Directional selection*

Most of the examples of adaptive evolution by major mutations mentioned previously do not appear to represent a shift between two adaptive zones, but rather a response to a changing environment that produced strong directional selection on some character, or strong selection for a new optimal phenotype. This is especially clear in the many cases of evolution of industrial melanism and pesticide resistance in insects.

The simplest model of directional selection is where relative fitness increases exponentially with increasing values of the character,

$$w(z) \propto e^{\beta z} \quad \text{or} \quad w(z) \propto e^{\beta(z-\bar{z})}. \tag{7}$$

This form of directional selection has the property that the selection differential on the background variation is always the same for all genotypes at the major locus, hence the polygenic background evolves at a constant rate,

$$\Delta \bar{z} = h^2 \sigma^2 \beta. \tag{8}$$

A constant relation is also maintained between the mean fitness components of the major locus genotypes,

$$\bar{w}_i / \bar{w}_0 = e^{\beta \alpha_i} \quad \text{for } i = 1, 2.$$

A recessive or dominant mutant, with major effect α and disadvantage s due to pleiotropic effects, will increase in frequency only if the intensity of directional selection and the magnitude of the mutant effect on the character are sufficiently large for the advantage gained in directional selection to overcome the disadvantageous pleiotropic effects,

$$(1-s)\, e^{\beta \alpha} > 1. \tag{9}$$

Given this condition, a recessive or dominant mutation will eventually be fixed in the population, after which further evolution of the character will continue by selection on the background polygenic variation.

The exponential model of directional selection also simplifies comparison of the relative rates at which a large phenotypic change in a population can be produced by the substitution of a major mutation versus the accumulation of numerous minor mutations. Assuming weak selection, such that $s < \beta\alpha \ll 1$, the net selective advantage of the major mutant in (9) is approximately $\beta\alpha - s$. Consider the time required for the frequency of the major mutant to evolve from a low value, $q_0 \ll \frac{1}{2}$, to an intermediate frequency such that the major mutant phenotype is in the majority in the population. Using general formulas in Crow and Kimura (1970 p. 193), the time in generations for a recessive or dominant mutation to make this transition is approximately $T \simeq 1/(\beta\alpha - s)q_0$ or $T \simeq (-\ln q_0)/(\beta\alpha - s)$ respectively. During the same transition, a semidominant mutation with $2\alpha_1 = \alpha_2 = \alpha$ and $2s_1 = s_2 = s$ under weak selection ($2\bar{w}_1/\bar{w}_0 \simeq \bar{w}_2/\bar{w}_0 \simeq 1 + \beta\alpha$) requires a time in generations of approximately $T \simeq (-2 \ln q_0)/(\beta\alpha - s)$. The time for a rare semidominant mutation to reach majority frequency in a population is much closer to that for a dominant mutation than a recessive one.

In comparison, the number of generations necessary to produce phenotypic evolution of the same magnitude, about $\alpha/2$, by selection on polygenic background variation is, from (8), $T = \alpha/(2h^2\sigma^2\beta)$.

A large evolutionary change in the mean phenotype in a population will occur more rapidly by a major mutation than by polygenic changes only if the initial frequency of the major mutant exceeds a critical value depending on its degree of dominance,

$$\text{recessive:} \quad q_0 > 2/b \tag{10a}$$

$$\text{semidominant:} \quad q_0 > e^{-b/4} \tag{10b}$$

$$\text{dominant:} \quad q_0 > e^{-b/2} \tag{10c}$$

where

$$b = (1 - s/\beta\alpha)\alpha^2/h^2\sigma^2.$$

This result for purely directional selection suggests that in a more realistic model of changing environments, where selection acts strongly toward a new optimal phenotype, the fixation of a major mutation that is initially rare may be prevented by the more rapid evolution of the optimal phenotype through polygenic changes. This problem is investigated in the next section for major mutations that are recessive or dominant.

(iii) *Selection toward a new optimum*

If the optimal phenotype in an adaptive zone changes or fluctuates slowly with time, it is obvious that mutations of small effect would permit a population to track the optimum more closely than mutations of large effect, and the latter would generally be selected against. We therefore model the genetic response of a population to a sudden and substantial change in the optimal phenotype, *e.g.*, after migration to a new habitat, or

alteration of the environment by industrial pollution or pest control treatments. If the change in the optimum phenotype occurs only for the character z, the pleiotropic effects of the major mutation on other characters (assumed to be initially at their optima) would not be beneficial ($s_1, s_2 \geqq 0$).

A simple form of selection toward an optimal phenotype, θ, is the Gaussian function

$$w(z) = \exp\{-\tfrac{1}{2}(z-\theta)^2/\omega^2\} \tag{11a}$$

where ω gives roughly the range of phenotypes around the optimum which have relatively high fitness. The components of the mean fitnesses for the major locus genotypes produced by selection on character z can then be computed as

$$\bar{w}_i = c \cdot \exp\{-\tfrac{1}{2}(\bar{z}+\alpha_i-\theta)^2/(\omega^2+\sigma^2)\} \quad \text{for } i = 0, 1, 2 \tag{11b}$$

in which c is a positive constant. The intensity of directional selection on background variation around each of the major locus genotypes is proportional to

$$\frac{\partial \bar{w}_i}{\partial \bar{z}} = -\left(\frac{\bar{z}+\alpha_i-\theta}{\omega^2+\sigma^2}\right)\bar{w}_i \quad \text{for } i = 0, 1, 2. \tag{11c}$$

Consider first a recessive mutation at the major locus, with $\alpha_1 = 0$, $\alpha_2 = \alpha$ (hence $\bar{w}_1 = \bar{w}_0$) and $s_1 = 0$, $s_2 = s$. There are two boundary equilibria, corresponding to loss or fixation of the major mutant allele, with the mean phenotype of the population at the optimum,

$$q = 0 \qquad \bar{z} = \theta \tag{12a}$$

and

$$q = 1 \qquad \bar{z} = \theta - \alpha. \tag{12b}$$

The equilibrium with $q = 0$ is always stable, but the stability of the equilibrium with the major mutation fixed depends on the existence of a third, internal equilibrium with $0 < q < 1$. At an internal equilibrium $\bar{w}_0 = (1-s)\bar{w}_2$ and $q^2\alpha = \theta - \bar{z}$, and using (11b) yields

$$\bar{z} = \theta - \frac{\alpha}{2} + \frac{\omega^2+\sigma^2}{\alpha}\ln(1-s) \tag{13a}$$

$$q = \sqrt{\frac{1}{2} - \frac{\omega^2+\sigma^2}{\alpha^2}\ln(1-s)}. \tag{13b}$$

Since the pleiotropic effects of the major mutant are assumed to be deleterious ($s \geqq 0$), the existence of the internal equilibrium ($q < 1$) implies

$$(1-s)\exp\{\tfrac{1}{2}\alpha^2/(\omega^2+\sigma^2)\} > 1. \tag{14a}$$

This condition requires that the selective advantage of the major effect exceed the disadvantage of the pleiotropic effects when the mean phenotype of the mutant homozygote is at the optimum,

$$(1-s)\bar{w}_2/\bar{w}_0|_{\bar{z}=\theta-\alpha} > 1. \tag{14b}$$

Local stability analysis indicated that when the internal equilibrium (13) exists it is always unstable, representing a saddle point in the surface of

$\bar{w}$ separating two adaptive peaks at the boundary equilibrium (12a, b). In this case some initial conditions lead to fixation of the major mutation and others lead to its loss from the population. Fig. 1 confirms the notion that, even under selection for a large phenotypic change, if the major mutation is initially rare, it may take so long to increase frequency that the new optimum phenotype is evolved more rapidly by polygenic changes and the major mutation will not be fixed.

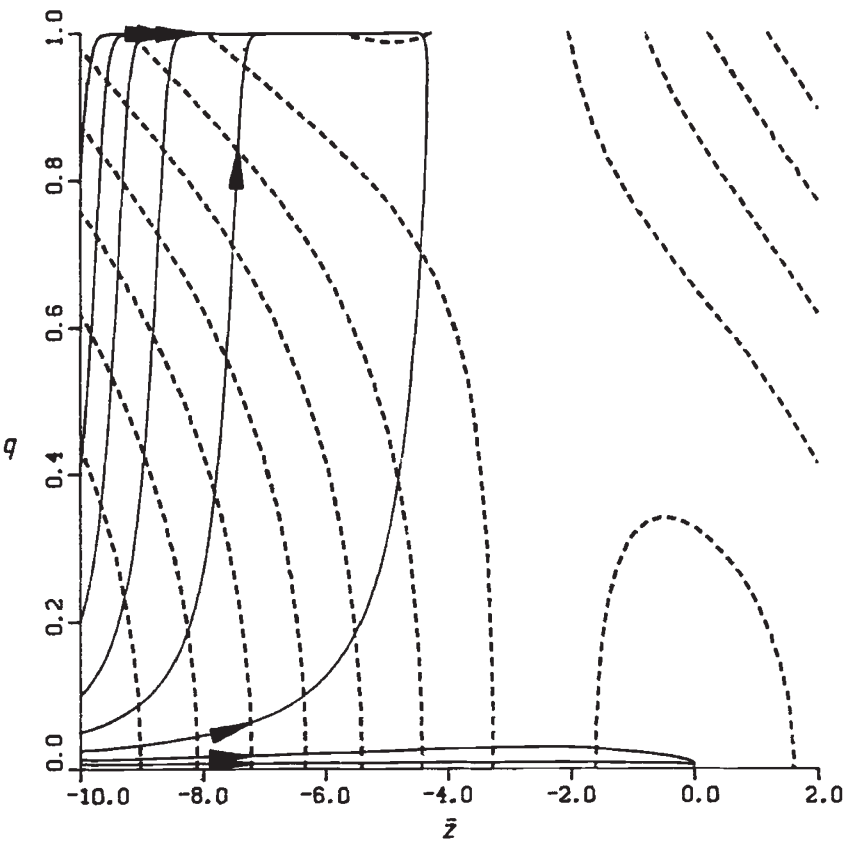

FIG. 1. Joint evolution of a major recessive mutation with frequency q, and polygenic modifiers with average effect $\bar{z}$, influencing a metrical trait. The character is under stabilizing selection toward an optimum phenotype at $\theta = 0$, by a Gaussian fitness function (equation (11a)) with $\omega^2 = 50$. In the absence of the major mutant the polygenic background has variance $\sigma^2 = 1$ and heritability $h^2 = 0{\cdot}5$. The effect of the major mutant on the character is $\alpha = 5{\cdot}0$ and the mutant homozygote has a pleiotropic disadvantage of $s = 0{\cdot}02$. There are two adaptive peaks in the surface of mean fitness indicated by the dashed contours, corresponding to loss and fixation of the major mutation. Initial conditions for the dynamic trajectories are $\bar{z} = -10{\cdot}0$ with $q = 0{\cdot}8$, $0{\cdot}4$, $0{\cdot}2$, $0{\cdot}1$, $0{\cdot}05$, $0{\cdot}025$, $0{\cdot}0125$, $0{\cdot}00625$.

When the internal equilibrium does not exist there is only one stable state for the population (12a), and the major mutation can never become fixed by selection. However, even in the latter case when the mean phenotype is initially far from the optimum the major mutation may increase in frequency before it is finally lost (fig. 2).

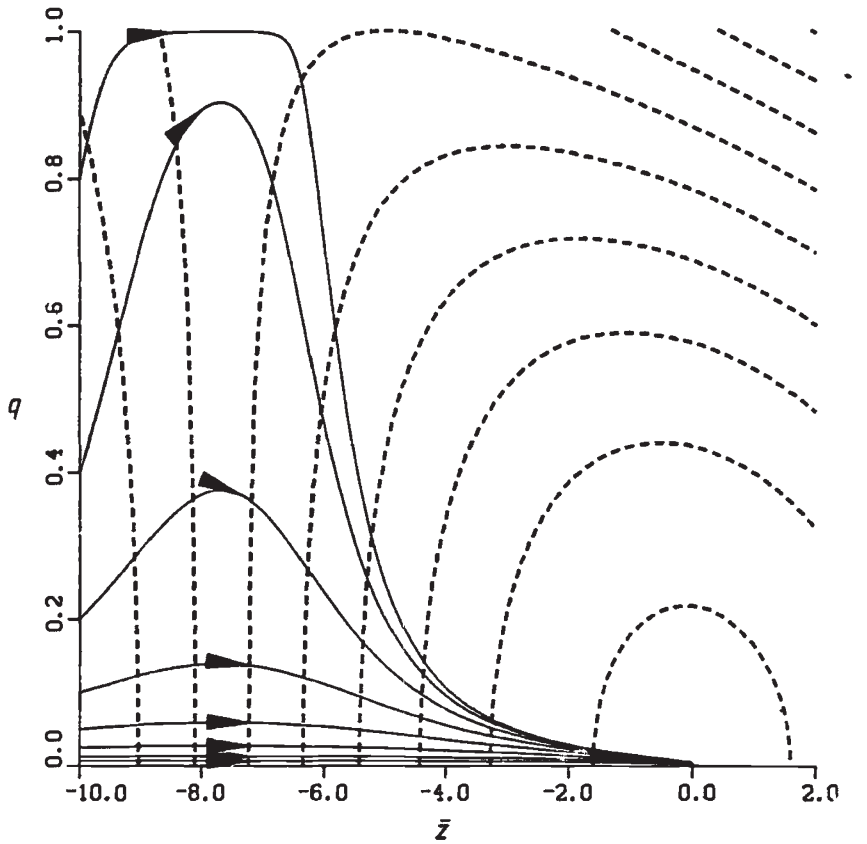

FIG. 2. The same as fig. 1 except that the major recessive mutant homozygote has a pleiotropic disadvantage of $s = 0{\cdot}40$. There is a single adaptive peak in the surface of mean fitness, corresponding to loss of the major mutation.

For a dominant mutation at the major locus, $\alpha_1 = \alpha_2$ (hence $\bar{w}_1 = \bar{w}_2$) and $s_1 = s_2$. Letting $\alpha_2 = \alpha$ and $s_2 = s$, again there are the two boundary equilibria (12a, b). An internal equilibrium requires $\bar{w}_0 = (1-s)\bar{w}_2$ and $[1-(1-q)^2]\alpha = \theta - \bar{z}$, which with (11b) yields the same value of $\bar{z}$ as in (13a) and

$$q = 1 - \sqrt{\frac{1}{2} + \frac{\omega^2 + \sigma^2}{\alpha^2} \ln(1-s)}. \tag{15}$$

Supposing that the pleiotropic effects of the major mutation are deleterious ($s \geqq 0$), existence of the internal equilibrium (q real) again implies (14). When the internal equilibrium exists it is always unstable, again representing a saddle point in the surface of $\bar{w}$ separating two adaptive peaks at the boundary equilibria (fig. 3). If the internal equilibrium does not exist the only stable equilibrium is that where the major mutation is lost from the population. Comparison of fig. 1 and fig. 3 indicates that for any initial state of the population, selective conditions favoring a rare major mutation are more likely to lead to fixation of a dominant mutation than a recessive one.

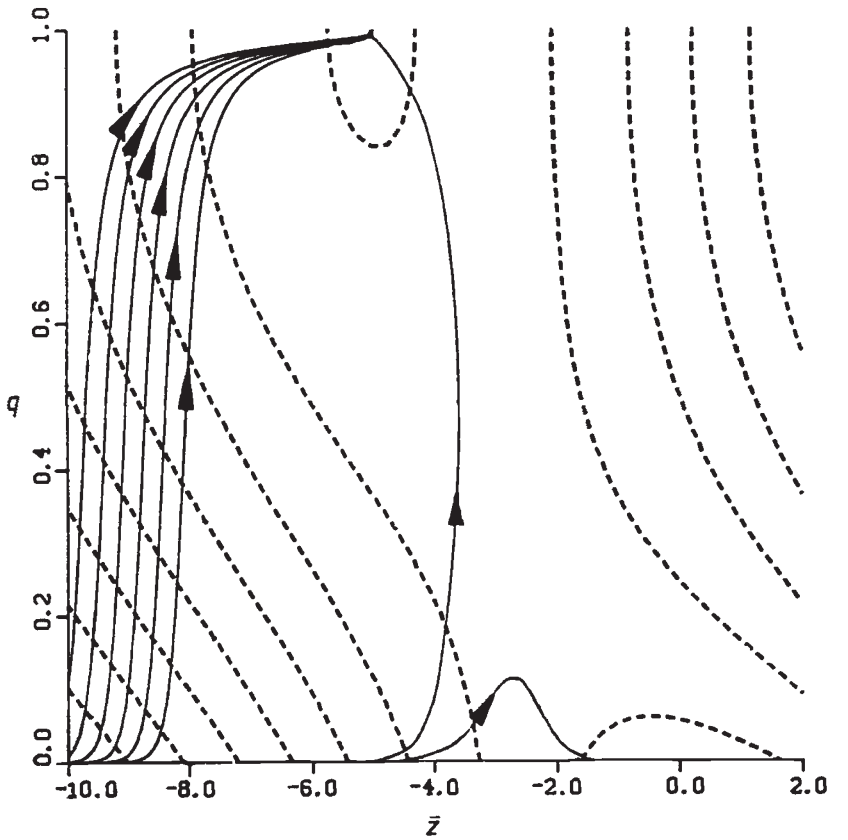

FIG. 3. Joint evolution of a major dominant mutation with frequency q, and polygenic modifiers with average effect $\bar{z}$, influencing a metrical trait. Parameters are otherwise the same as in fig. 1, except that the initial conditions for the dynamic trajectories are $\bar{z} = -10{\cdot}0$ with $q = 0{\cdot}1$, $0{\cdot}01$, $0{\cdot}001$, 10^{-4}, 10^{-5}, 10^{-6}, and $\bar{z} = -6{\cdot}0$ with $q = 10^{-5}$, 10^{-6}. In comparison to a major recessive mutation with all else equal (fig. 1), a major dominant mutation is more likely to be fixed even when the initial frequency of the former is orders of magnitude higher than that of the latter.

Stable polymorphism for a recessive or dominant major mutation within a population is not possible unless selection on the genotypes at the major locus is frequency-dependent, as it is for mimicry polymorphisms (Ford, 1975) and the major sex-determining locus in many higher animals (Fisher, 1958 pp. 158–160).

4. CONDITIONS FOR ADAPTIVE POLYMORPHISM OF A MAJOR MUTATION

The situation most conducive to stable adaptive polymorphism of a gene with major effect might seem to be that where the heterozygote is phenotypically distinct from both homozygotes, as with partial dominance or overdominance, so that selection could favor the heterozygote. But this argument ignores the influence of polygenic background variation, which makes the conditions for the maintenance of a major polymorphism rather extreme. This section demonstrates that under weak optimizing selection

no stable adaptive polymorphism can be maintained for a semidominant gene of major effect (assuming that its pleiotropic effects are deleterious). It is also shown that, regardless of the degree of dominance of the major mutation, if there is no selection on its pleiotropic effects then a stable polymorphism can not be maintained under weak optimizing selection. An example is given of a stable polymorphism maintained by strong optimizing selection favoring the heterozygous effect of a mutation with pleiotropic effects that render the homozygote lethal.

(i) *Weak selection toward an optimum phenotype*

Under weak stabilizing selection toward an optimum phenotype, θ, the Gaussian fitness function (11a) acting on the character can be approximated as quadratic

$$w(z) = 1 - k(z-\theta)^2 \tag{16a}$$

in which $k = 1/2\omega^2$. This produces components of mean fitness for the major locus genotypes of

$$\bar{w}_i = 1 - k[(\bar{z} + \alpha_i - \theta)^2 + \sigma^2] \quad \text{for } i = 0, 1, 2. \tag{16b}$$

Assuming that selection on the pleiotropic effects of the major mutation are also weak ($s_1, s_2 \ll 1$), the mean fitness in the entire population can be written approximately by neglecting terms of order ks_1 and ks_2 as

$$\bar{w} = 1 - k[(\bar{\bar{z}} - \theta)^2 + V + \sigma^2] - 2q(1-q)s_1 - q^2 s_2 \tag{16c}$$

in which $\bar{\bar{z}}$ represents the grand mean of the character and V is the variance in the character created by polymorphism at the major locus (cf. Wright, 1935).

For a semidominant major mutation with $2\alpha_1 = \alpha_2 = \alpha$ the grand mean phenotype and the contribution to the genetic variance are

$$\bar{\bar{z}} = \bar{z} + \alpha q \quad \text{and} \quad V = q(1-q)\alpha^2/2.$$

In addition to the two boundary equilibria in (12), application of equations (4) indicates that there is a polymorphic equilibrium at $\bar{z} = \theta - \alpha q$ and

$$q = \frac{k\alpha^2 + 4s_1}{2(k\alpha^2 + 4s_1 - 2s_2)}.$$

Assuming that the pleiotropic effects of the major mutation are not beneficial ($s_1, s_2 \geqq 0$), this equilibrium exists ($0 < q < 1$) if the following condition is satisfied,

$$k\alpha^2 > -4s_1 + 4s_2. \tag{17}$$

The condition for stability of this equilibrium is that at this point $\bar{w}$ should be a local maximum, which means that the matrix

$$\begin{pmatrix} \dfrac{\partial^2 \bar{w}}{\partial q^2} & \dfrac{\partial^2 \bar{w}}{\partial \bar{z}\, \partial q} \\ \dfrac{\partial^2 \bar{w}}{\partial q\, \partial \bar{z}} & \dfrac{\partial^2 \bar{w}}{\partial \bar{z}^2} \end{pmatrix} = \begin{pmatrix} -k\alpha^2 + 4s_1 - 2s_2 & -2k\alpha \\ -2k\alpha & -2k \end{pmatrix}$$

should be negative definite. This implies both that $k\alpha^2 > 4s_1 - 2s_2$ and

$k\alpha^2 < -4s_1 + 2s_2$. But the second of these conditions is inconsistent with (17). Therefore a stable adaptive polymorphism cannot be maintained by weak optimizing selection on a major semidominant mutation with pleiotropic effects that are deleterious or selectively neutral.

When the degree of dominance is arbitrary the grand mean of the character in the population is

$$\bar{\bar{z}} = \bar{z} + 2q(1-q)\alpha_1 + q^2\alpha_2 \tag{18a}$$

and it is convenient to express the variance contributed by the major locus in terms of the quantities $a = a_2/2$ and $d = \alpha_1 - \alpha_2/2$ (Falconer, 1981 pp. 115–118),

$$V = 2q(1-q)[a + (1-2q)d]^2 + [2q(1-q)d]^2. \tag{18b}$$

To demonstrate the instability of an equilibrium with the major locus polymorphic, in view of (6) it is sufficient to prove that the selective surface is not a local maximum at the equilibrium. The condition for equilibrium (from 4b), $\partial\bar{w}/\partial\bar{z} = 0$, applied to (16c) reveals that the grand mean phenotype is at the optimum, $\bar{\bar{z}} = \theta$. In conjunction with (18a) this equation defines a quadratic curve relating $\bar{z}$ to q, on which any polymorphic equilibrium point must lie. A necessary (but not sufficient) condition for such an equilibrium to be stable is that the curvature of the adaptive topography along this line, evaluated at the equilibrium point, must be negative. Provided there is no selection on the pleiotropic effects of the major mutation ($s_1 = s_2 = 0$), it can be seen from equations (16c) and (18b) that this criterion is not satisfied at any point since

$$\left.\frac{d^2\bar{w}}{dq^2}\right|_{\bar{z}=\theta} = 4k[a + 3(1-2q)d]^2 + 24k(1-2q)^2 d^2 > 0. \tag{19}$$

Thus when optimizing selection acts only on the main effect of a major mutation a stable polymorphism cannot exist since the adaptive topography is not a local maximum at any point along the curve $\bar{\bar{z}} = \theta$. This result extends the work of Fisher (1958 pp. 118–121) and Bulmer (1971), who reached the same conclusion for a mutation of small effect and arbitrary dominance.

(ii) *Strong selection for the heterozygous effect of a homozygous lethal mutation*

In some natural and artificial populations an adaptive polymorphism has been created by selection for the heterozygous effect of a mutation that is lethal as a homozygote. The gene for sickle-cell anemia in man reaches frequencies of up to 24 per cent in areas where malaria is endemic, although homozygotes generally die before adulthood (Cavalli-Sforza and Bodmer, 1971). The major gene for Warfarin resistance in rats occurs in frequencies up to about one third in many areas of Europe despite being nearly lethal as a homozygote (Greaves and Ayres, 1969, 1976, 1977; Greaves *et al.*, 1977). Industrial melanism in the moth *Phigalia pedaria* is produced by two different dominant alleles at a single locus, one of which, while lethal as a homozygote, reaches frequencies of 15 per cent in some areas in England (Ford, 1975 p. 339).

Similar polymorphisms are sometimes produced in artificial selection experiments. During selection for small body size in a mouse population (MacArthur, 1949) a partially dominant major gene for dwarfism increased to intermediate frequency despite sterility of the homozygotes. Artificial selection on *Drosophila melanogaster* for increased abdominal bristle number created a balanced polymorphism for a gene with a major heterozygous effect on bristle number, but which was lethal as a homozygote (Clayton, Morris and Robertson, 1957; see also Frankham, Jones and Barker, 1968). These experiments are reviewed by Falconer (1981 pp. 203–206).

For a mutation that has a lethal pleiotropic effect when homozygous, $s_2 = 1$, the primary effect of the homozygote on the quantitative character (α_2 or $\bar{w}_2$) is immaterial. Let $s_1 = s$ and $\alpha_1 = \alpha$, and assume selection toward an optimal phenotype by a Gaussian fitness function (11a). Fixation of the mutant allele is impossible because as $q \to 1$, $\bar{w} \to 0$ and $\Delta q \to -\frac{1}{2}$. There is a single boundary equilibrium at $q = 0$ and $\bar{z} = \theta$. The conditions for an equilibrium with polymorphism at the major locus are

$$q = \frac{(1-s)\bar{w}_1 - \bar{w}_0}{2(1-s)\bar{w}_1 - \bar{w}_0} \tag{20a}$$

and $2q\alpha = \theta - \bar{z}$ which, together with (11b), yield the equation for q,

$$\frac{(1-s)(1-2q)}{(1-q)} = \exp\left\{\frac{\alpha^2(1-4q)}{2(\omega^2+\sigma^2)}\right\}. \tag{20b}$$

If stabilizing selection is sufficiently strong, and the heterozygous effect of the mutation on the quantitative trait is large enough, $\alpha^2 \gg \omega^2 + \sigma^2$, there are two possible solutions to this equation. Assuming that the pleiotropic effects of the heterozygote are not beneficial ($s \geqq 0$), inspection of (20b) indicates that at a polymorphic equilibrium the frequency of the major mutant must lie in the range

$$\tfrac{1}{4} < q < \tfrac{1}{2}. \tag{21a}$$

Substituting $q > \frac{1}{4}$ into (20a) reveals that at equilibrium the heterozygote must have a net fitness at least 50 per cent greater than that of the nonmutant homozygote,

$$(1-s)\bar{w}_1/\bar{w}_0 > \tfrac{3}{2}. \tag{21b}$$

When these two polymorphic equilibria exist, fig. 4 shows that the one with the higher frequency of the mutant allele is stable and the other is unstable.

Although the model is probably not very accurate under such strong selection, it does suggest that the presence of polygenic background variation sets rather stringent conditions for the existence of a stable adaptive polymorphism involving a homozygous lethal gene. The requirement of strong optimizing selection favoring the heterozygote, and the restricted range of possible mutant gene frequency, contrasts with the usual model of a single homozygous lethal mutation (with no polygenic background) in which any amount of heterozygote advantage produces a balanced polymorphism with an equilibrium frequency in the range $0 < q < \frac{1}{2}$.

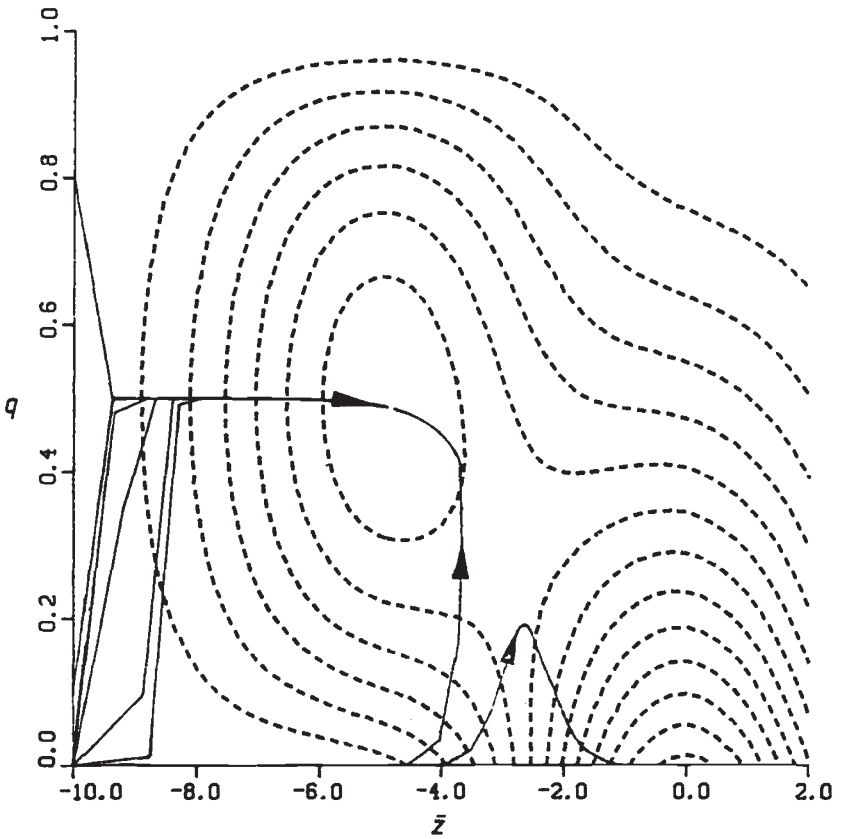

FIG. 4. Joint evolution of a recessive lethal mutation and polygenic modifiers influencing a metrical trait. The major mutant has a heterozygous effect of $\alpha = 5{\cdot}0$ on the character, with deleterious effects only in the homozygote. The polygenic background has variance $\sigma^2 = 1$ and heritability $h^2 = 0{\cdot}5$. Intense stabilizing selection toward an optimal phenotype $\theta = 0$ occurs by a Gaussian fitness function (equation (11a)) with $\omega^2 = 3$. There are two adaptive peaks in the surface of mean fitness indicated by the dashed contours, corresponding to loss and stable polymorphism of the recessive lethal mutation. Initial conditions for the dynamic trajectories are $\bar{z} = -10{\cdot}0$ with $q = 0{\cdot}8$, $0{\cdot}1$, $0{\cdot}001$, 10^{-4}, 10^{-5}, 10^{-6}, and $\bar{z} = -6{\cdot}0$ with $q = 10^{-6}$, 10^{-7}.

That the frequency of the sickle-cell gene in human populations is less than $\frac{1}{4}$, and the relative fitness of the heterozygote is less than $\frac{3}{2}$ even in the presence of malaria, implies either that the system is not an evolutionary equilibrium, perhaps due to immigration from nonresistant populations (Cavalli-Sforza and Bodmer, 1971, Chapter 4), or that there is no appreciable polygenic variation for resistance ($h^2\sigma^2 \simeq 0$).

This model provides a better description of the evolution of Warfarin resistance in some rat populations, in which the major mutation attained a stable frequency of about one third, with the fitness of the heterozygote at least 50 per cent larger than that of the susceptible homozygote. In this case the expression of the major mutant was subject to modification by selection on background genetic variation (Greaves and Ayres, 1976; Greaves *et al.*, 1977).

5. Discussion

Evolution into a new adaptive zone may sometimes be accomplished by a major mutation, when evolution of the new adaptive phenotype by small increments would be selected against. This appears to have occurred in the evolution of interspecific mimicry (Charlesworth and Charlesworth, 1975; Turner, 1977, 1981), and may also happen with appreciable frequency during adaptive radiations when many new ecological niches are available (Wright, 1978 Chapter 12).

In a changing environment, evolution toward a single optimum phenotype typically involves the mutual adjustment of many characters of a population. The greater probability of producing adaptive changes, and the much larger spontaneous rates of minor mutations compared to major mutations, implies that a population can track a slowly changing optimum phenotype most closely in the usual Darwinian mode, by a series of small steps.

A sudden change in the optimum phenotype in an adaptive zone can create strong selection for a major phenotypic change, sustained over several generations. If selection for the main effect of a major mutation is sufficiently strong to overcome its deleterious pleiotropic effects, it may be fixed in a population before the new optimum phenotype can be built up by accumulation of minor mutations.

Drastic alterations of the environment within a few generations often occur in domesticated populations subject to outbreaks of pests and diseases, and in artificially disturbed populations, such as those affected by pollution and by chemical and biological control agents. Fluctuations in the biotic and physical environment of most natural populations are probably not often so extreme, because of previous adaptation and coevolution. These conclusions help to explain why major mutations are more frequently fixed in domesticated and artificially disturbed populations than in natural ones.

The degree of dominance of a major mutation in part determines its evolutionary potential in the presence of minor mutations. For most characters, particularly morphological traits, major mutations are most often largely recessive, and are usually degenerative, reducing the expression of the character. These patterns are clearly illustrated by the inheritance of major mutations affecting various parts of the body in *Drosophila* (Braver, 1956; Lindsley and Grell, 1968) and mice (Green, 1975; King, 1975). Exceptions to these rules do occur for some characters, such as melanic coloration in insects, for which most major mutations are dominant (Ford, 1975 Chapter 14). It is also noteworthy that different pleiotropic effects of a major mutation may display different degrees of dominance (Caspari, 1952; Greaves *et al.*, 1977). Although the initial frequency maintained by recurrent mutation is much higher for a recessive mutant than for a dominant one, with all else equal (Crow and Kimura, 1970 Chapter 6), numerical analysis of the present models indicated that following a sudden change in the optimal phenotype in an adaptive zone, a partially or fully dominant major mutation is more likely to be fixed than is a completely recessive mutation.

The models also reveal the difficulty of maintaining an adaptive polymorphism for a major mutation in the presence of polygenic variation. In

the absence of frequency-dependent selection, a stable polymorphism cannot exist for a fully dominant or recessive major mutation. It might be thought at first that stabilizing selection toward an intermediate phenotype could confer a heterozygote advantage on a partially dominant mutation, producing a stable polymorphism. But in contrast to the one-locus situation, where heterozygote advantage is sufficient to produce adaptive polymorphism, polygenic variation destabilizes polymorphism of a major mutation. Under weak stabilizing selection toward an optimum phenotype, a stable adaptive polymorphism for a major semidominant mutation cannot be maintained. An intuitive explanation for this result is that the optimum phenotype can be more nearly achieved by most individuals in the population based on minor mutations, while avoiding the segregation load produced by polymorphism of the major mutation. It has nevertheless been shown here that in the extreme situation of strong stabilizing selection favouring the heterozygous effects of a recessive lethal mutation, a major adaptive polymorphism can be maintained in the presence of polygenic variation.

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