DISTRIBUTION OF EFFECTS OF NEW MUTATIONS AFFECTING QUANTITATIVE TRAITS

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SUMMARY

Departures from assumptions of additive, symmetrical, normal and non-pleiotropic distributions of effects of mutations affecting quantitative traits are discussed with respect to theoretical models predicting long-term response to directional selection, divergence between populations and maintenance of quantitative genetic variation within populations. That these assumptions may be violated is inferred from observations of long-term selection response, studies of the effects of spontaneous and induced mutations on quantitative traits, and mapping quantitative trait loci. The results of an experiment are presented in which the effects of new, stable *P* element insertions, in an inbred host background originally free of *P* elements, were determined on viability and two bristle traits in *Drosophila*. The distributions of homozygous effects of the new insertions on the bristle traits are skewed and highly leptokurtotic. The effects are mostly recessive, and show pleiotropy in that both bristle traits are sometimes affected and viability is reduced.

INTRODUCTION

Recent models have stressed the importance of the contribution of new mutations to long-term response of quantitative traits to directional selection (Hill, 1982a,b; Keightley and Hill, 1983, 1987; Zeng and Hill, 1986) and to variation of quantitative traits within and among natural populations (Lande, 1975; Turelli, 1984, 1985; Barton, 1986; Lynch and Hill, 1986; Cockerham and Tachida, 1987; Slatkin, 1987; Keightley and Hill, 1988; Wagner, 1989). The model predictions vary according to whether population size is assumed to be infinite or finite, and whether directional, stabilizing, or no selection is assumed. Predictions also strongly depend on assumptions about the number of loci controlling quantitative traits, the mutation rates and variance of mutational effects per locus, the shape of the distribution of mutant effects, the heterozygous effects of new mutations, and pleiotropic effects of mutants on other traits and fitness. The theoretical predictions are discussed below, and evidence is presented that mutant effects on quantitative traits may be non-additive and pleiotropic, with skewed and highly leptokurtic distributions.

THEORY

Neutral model. Lynch and Hill (1986) derived the equilibrium genetic variance for a quantitative trait within, and the divergence in mean phenotype between, finite populations in which the input of variation from mutation is balanced by loss from genetic drift. The asymptotic rate of divergence is $2V_m$, where V_m is the input of new variance by mutation per generation, regardless of

the degree of dominance of new mutations, but the absolute amount of divergence at any time depends strongly on the dominance properties of the new mutations. The amount of divergence is greater for mutations which are fully dominant, and less for recessive mutations, than for purely additive new mutants. Similarly, the equilibrium genetic variance within a population is $2NV_m$ (N is the effective population size) whether mutations are additive or fully recessive, and a little greater than twice this if they are dominant. At any time during the approach to equilibrium the variance within populations is less for recessive and greater for dominant mutations than for additive new mutants. These conclusions hold for any distribution of mutant effects.

Response to directional selection. The asymptotic rate of response to directional selection from fixing new additive mutants with a distribution of mutant effects symmetric about zero is $2NiV_m\sigma_p$ (i is the standardized selection differential and σ_p the phenotypic standard deviation of the trait) (Hill, 1982a). For dominant mutations with a symmetrical distribution of effects, the rate is nearly half that of additive mutations, whereas recessive mutants contribute less response , at a rate proportional to $(Ni)^{1/2}$, and response occurs at a later time than for additive and dominant mutants (Hill, 1982a,b). If the mutants are not symmetrically distributed about zero, response depends on the mean square of effects of mutants affecting the trait in the direction of selection. The expected response from fixing new additive mutants is reduced if the distribution of effects is strongly leptokurtic, but the initial response and the variance of response is greater if the distribution of mutant effects has high variance or is leptokurtic (Hill, 1982a,b). With small populations and a highly variable or strongly leptokurtic distribution of additive mutant effects, sudden jumps in cumulative response due to the appearance and fixation of genes of large effect may be observed in some replicates but not others, leading to high variance in response. In contrast, mutational distributions with lower variance of effects give more regular and less variable patterns of response (Hill, 1982a,b). The expected and cumulated responses contributed by dominant and recessive new mutations are reduced further if they come from a highly variable or leptokurtic distribution of effects (Hill, 1982a,b). If in addition new mutations affecting the selected quantitative trait have an associated deleterious pleiotropic effect on fitness, the response to selection is less than the case where the new mutants are not associated with fitness. The extent of the reduction in response depends on the strength of the correlation of the joint effects on the trait and fitness (being greater for higher correlations) and on the intensity of artificial selection (being proportionately less for greater selection intensities) (Hill and Keightley, 1988). The variance maintained until fixation in this model is less than for neutral mutations under directional selection, but the reduction in variance due to pleiotropic fitness effects is less than the reduction in response.

Stabilizing selection. The predicted levels of genetic variance for a quantitative trait maintained within a population when an equilibrium is reached between the input of new mutants affecting the trait and loss by stabilizing natural selection is especially sensitive to model assumptions. For example, for an infinite popultion model of n mutationally equivalent loci with a variance of normally distributed, additive mutational effects much smaller than the variance of effects of segregating alleles, and stabilizing selection is a weak force relative to mutation, the genetic variance maintained by a balance of mutation and stabilizing selection is $(2nV_mV_s)^{1/2}$ (Lande, 1975), where V_s quantifies the strength of stabilizing selection (Slatkin, 1987). However, if stabilizing

selection is strong compared to mutation, and the effect of new mutations is large compared with existing variation, the equilibrium genetic variance maintained in an infinite population at n mutationally equivalent loci is $4\gamma V_s$, where γ is the number of new mutants per generation (Turelli, 1984). With this model the variance maintained is independent of the number and effects of alleles and the distribution of mutational effects, and is much less than that predicted by the Lande (1975) model because the equilibrium variance at each locus occurs when one of the alleles is near fixation.

The equilibrium variance maintained in a finite population by a balance of mutation and stabilizing selection is usually less than that maintained in an infinite population because new mutants may be lost by drift as well as selection (Keightley and Hill, 1988), and unlike the infinite population case both the scale and the shape of the distribution of additive mutant effects distributed symmetrically about zero affect the level of equilibrium genetic variance. For infinitesimally small mutational effects, genetic variance approaches the neutral level of $2NV_m$, but as the variance of mutant effects increases, genetic variance tends to zero, since they will be eliminated by stabilizing selection. For a highly leptokurtic distribution of effects, the variance maintained is less than half that of an infinite population; the extent of the reduction is greater the smaller the population (Keightley and Hill, 1988). Asymmetrical (skewed) distributions of mutant effects lead to lower levels of variance maintained in this model, because the population mean is moved away from the optimum and stabilizing selection is therefore stronger against most new mutants.

The effect of pleiotropy on the maintenance of variation by mutation - stabilizing selection balance on several characters depends on whether selection is a weak or a strong force compared to mutation. For weak selection and a multivariate normal distribution of uncorrelated mutant effects which are small compared to segregating variance, significant genetic variance can be maintained if characters related by pleiotropy are jointly subject to stabilizing selection (Lande, 1980). However, when selection is strong relative to mutation and the effects of new mutations are large compared to existing variation, pleiotropy between characters seriously reduces the equilibrium variance maintained for each trait whether or not the traits are correlated (Turelli, 1985). This is because the intensity of stabilizing selection on a mutant allele through its effect on a single trait is likely to be much less than the total intensity of selection on the allele through its effects on all traits. The contrast between the two model predictions comes about because the number and distribution of mutant effects per locus differs. In the first model many alleles with uncorrelated pleiotropic effects are assumed, so the traits respond independently to stabilizing selection. In the second the number of alleles per locus is small, with most variance contributed by rare alleles, so the pleiotropic effects are constrained (Turelli, 1985). Constrained pleiotropic effects may also occur among alleles at a locus because of interactions with other loci in the same developmental pathway (Wagner, 1989).

The effect of pleiotropy on variance maintained by mutation - selection balance can be deduced more simply by considering that a mutant allele has an effect on the metric, and a pleiotropic effect on fitness, where fitness takes into account the effect on all other characters determining the survival and reproduction of the individual (Hill and Keightley, 1988; Keightley and Hill, unpublished). Selection against the mutant is not necessarily stabilizing, as the fitness effect is a property of the mutant and not its effect on the deviation from an optimal phenotype, although it becomes eqivalent to stabilizing if the correlation of absolute effects on the trait and fitness approaches unity. When this correlation is less than one, there is no limit to the genetic variance maintained as N approaches infinity, because mutants with a large effect on the

trait that are neutral with respect to fitness contribute much variance when they occur in large populations (Keightley and Hill, unpublished).

INFERENCES

What inferences can be drawn from available data about the variance of mutational effects per locus, the shape of the distribution of mutant effects, heterozygous effects of new mutations, and pleiotropic effects of mutants with other traits and fitness? Some inferences can be made from the pattern of long-term selection response and analysis of highly selected lines, but the most useful sort of experiments are those in which mutations have been accumulated in initially isogenic populations. The input of mutational variance per generation can then be estimated from divergence among replicated sublines from the same isogenic base population, or from response to selection of an originally inbred strain. In the special case of *Drosophila*, entire replicated isogenic chromosomes can accumulate mutations independently while maintained as heterozygotes against a dominantly marked balancer chromosome; this allows the preservation of mutations with recessive deleterious fitness effects and prevents loss of new mutations by recombination and drift. Lynch (1988) has summarized V_m estimates from a number of traits and organisms. The estimates range from 0.0001–0.03 V_e (V_e is the environmental variance), with an average value of 0.004 V_e. However, V_m is a composite parameter of the number of loci affecting the trait, per locus mutation rate, and variance of mutational effects at each locus, so no information is gained about its individual components. The estimates may also be biased, perhaps considerably, if the assumptions of neutral, additive, symmetrically distributed mutations are violated.

Genes of large effect. Robertson (1967) argued that the most likely shape of the distribution of gene effects is leptokurtic with high variance because there are a very large number of loci at which mutations can occur; most will have little or no effects on the trait, but a few will have large effects. Turelli's (1984) assumption of a large variance of mutant effects relative to the standing variation predicts the distribution of segregating alleles will become leptokurtic, with most variance contributed by rare alleles (Turelli, 1988). There are several lines of evidence that mutations of large effect on quantitative traits do occur, and in some cases may segregate in natural populations. Alleles of major effect on the selected trait have often been observed in selection lines. In *Drosophila* lines selected for bristle score, *bobbed* (Clayton and Robertson, 1957 (probably); Frankham *et al.*, 1978), *scabrous* (Jones *et al.*, 1968; Yoo, 1980b), *scute* (Yoo, 1980b) and possibly *Delta* (Yoo, 1980b) alleles have appeared. Frankham and Nurthen (1981) discovered a *smooth* mutation segregating in a natural population of *Drosophila* at a frequency of 0.008. In mice selected for body size, *pygmy* (Falconer, 1989a) and other obese and dwarf mutants (Roberts and Smith, 1982) have often been observed; Bradford and Famula (1984) documented a new gene (*hg*) causing rapid postweaning weight gain in mice selected for this trait. Other genes of large effect discovered in domestic species are the double muscling gene in cattle (Hanset, 1982), the halothane gene in pigs (Webb *et al.*, 1982) and the Booroola gene in sheep (Piper and Bindon, 1982).

Indirect evidence for genes of large effects on quantitative traits comes from long-term selection experiments. If gene effects are small, response to selection from new mutations will be regular, but initially rare genes of large effect will cause a perceptible jump in response as they proceed to fixation, followed by a period of stasis or small increments in response. Variation among

replicate long-term selection lines is also expected if gene effects are occasionally large, from response from existing variation (rare genes of large effect will be present in some lines, but missed by sampling in the rest) and from new mutants of large effect. Repeated patterns of plateaux, followed by sudden, often dramatic, jumps in response, as well as great variation among replicates in response, are typical of the majority of documented long-term responses (Clayton and Robertson, 1957; Thoday and Boam, 1961; Roberts, 1966; Falconer, 1971; Sheldon and Milton, 1972; Enfield, 1977, 1980; Yoo, 1980a; Sheldon and Evans, 1981). Evidence from response of initially isogenic populations to directional selection from spontaneous or X-ray-induced mutations is more scarce. There are only a few such experiments in *Drosophila* (Mather and Wigan, 1942; Clayton and Robertson, 1955, 1964; Kitagawa, 1967; Hollingdale and Barker, 1971). When selection is monitored over 20 generations or so, response from new mutations is small, and relatively smooth (Mather and Wigan, 1942; Hollingdale and Barker, 1971), but over a time scale of 50 generations or more response proceeds in jumps (Mather and Wigan, 1942), as would be expected if the distribution of mutant effects was leptokurtic. The results of an experiment in which three replicates of divergent selection for abdominal and for sternopleural bristle score were started from a highly inbred line and continued for over 80 generations (T. F. C. Mackay, R. F. Lyman, and M. S. Jackson, unpublished data) also show clear jumps in response and variance between replicates in response.

Similar patterns are also observed in selection lines started from crosses of *Drosophila* strains in which *P* transposable elements are mobilized (Mackay, 1985a; Torkamanzehi *et al.*, 1988; Pignatelli and Mackay, 1989), suggesting that transposable element-induced mutations may also have large effect on quantitative traits. Lai and Mackay (1990) mutagenized isogenic *Drosophila X* chromosomes by *P* element mutagenesis. Most of the increase of variance for two bristle traits among the mutagenized chromosomes was caused by a few lines with large (1.5 – 3.0 σ_p) effects.

Evidence that genes of large effect contribute to selection response for sternopleural bristle score in *Drosophila* also comes from attempts to map the loci contributing to the difference in score between divergent selection lines. The overall effect of a chromosome extracted from a selection line can be partitioned into regions by recombination with a multiply marked chromosome, and the effect of each region assessed (Thoday, 1961). In general few genes have been found to account for most of the selection response. Thoday and his colleagues (reviewed by Thoday, 1979) located 9 major sternopleural bristle effects distributed over all major chromosomes. Shrimpton and Robertson (1988a,b) found that 17 factors accounted for a difference in score of 24 sternopleural bristles between high and low selection lines; the largest effect was $1.8\sigma_p$ (located close to or at the *hairy* locus, some alleles of which affect bristle score). The distribution of effects was skewed, with increasing frequency of effects to the limit of ascertainment of $0.5\sigma_p$. Three or four factors accounted for a third of the difference in score.

Symmetry of effects. Evidence on whether or not mutational effects are symmetrically distributed about a mean of zero is from symmetry of response to directional selection and change of mean phenotype over time of an originally isogenic population allowed to accumulate spontaneous or induced mutations. It is clear that mutations affecting fitness and its components are deleterious. Simmons and Crow (1977) summarize the evidence from accumulation of spontaneous and induced viability mutations on replicate isogenic *Drosophila* chromosomes sheltered from natural selection by a balancer chromosome, viability mutations on chromosomes extracted from natural populations, and induced and spontaneous

mutations affecting fitness. The effect of mutations on total fitness exceeds their effect on the viability component alone, and in all cases the mutations reduce fitness and its components. Transposable-element-induced mutations have similar skewed distributions of effects on viability and total fitness (Yukuhiro *et al.*, 1985; Fitzpatrick and Sved, 1986; Mackay, 1986).

Traits not closely associated with fitness may have a more symmetrical distribution of effects - at least the tendency of traits such as *Drosophila* bristle number to respond roughly equally to short-term selection for increased or decreased numbers from a segregating base population (Clayton *et al.*, 1957) indicates alleles of increasing and decreasing effect are present in natural populations. Later asymmetrical responses to divergent selection cannot be taken as evidence for asymmetrical effects, because they could be attributable to differences in gene frequency, dominance, scale, or natural selection (Falconer, 1989b). Because the alleles contributing to selection response in a segregating population have already been screened by natural selection, it is possible they do not represent the original distribution of effects. Therefore observations on the effects of new spontaneous or induced mutations are critical, but little information of this sort exists. There is some evidence that spontaneous mutations affecting *Drosophila* bristle score do not change the population mean, suggesting symmetrical mutational distributions for these traits. The spontaneous mutation control lines of Kitagawa (1967) remained stable for 20 generations. The mean abdominal and sternopleural bristle scores of 25 independent sublines started from a highly inbred base population decreased very little over an 80 generation period of mutation accumulation - 0.006 abdominal and 0.009 sternopleural bristles per generation (T. F. C. Mackay, R. F. Lyman, M. S. Jackson, and C. Terzian, unpublished). Asymmetrical responses to divergent selection from an inbred base may point to asymmetry in the underlying mutational distribution. However, only the experiment of Mather and Wigan (1942) and the one by Mackay *et al.* (unpublished) described above yield information bearing on this point. (The others were either not continued for sufficiently long for response to be appreciable, selected in one direction only, or did not present the relevant data). In both cases there is evidence of asymmetry of response, albeit in no consistent pattern. Mather and Wigan (1942) consistently achieved greater response for high than low abdominal bristle score. The average response of the high abdominal bristle selection lines in the experiment of Mackay *et al.* (unpublished) is 2.0 bristles, and of the low lines is 8.9 bristles; the mean response of the high sternopleural selection lines is 4.2 bristles, whereas the low sternopleural lines average 1.6 bristles. Lai and Mackay (1990) used *P* element mutagenesis to induce mutations on inbred *Drosophila X* chromosomes, and found all mutants reduced abdominal or sternopleural bristle score.

Heterozygous effects. A large number of estimates of the heterozygous effects of mutations affecting viability in *Drosophila* have been accumulated, both from equilibrium populations and induced mutations (summarized by Simmons and Crow, 1977). Lethal mutations are not completely recessive, and decrease heterozygous viability by 1-3%. Mildly detrimental viability mutations are more nearly additive, decreasing heterozygous viability by 30-50%. There is thus an association between homozygous effect and degree of dominance for viability mutations; mutations with extreme homozygous effects are more recessive. The effect of new mutations on heterozygous fitness is more severe, with a heterozygous fitness reduction equal to the homozygous viability effect.

Less information is known of the dominance properties of quantitative traits less closely associated with fitness. In *Drosophila*, most major morphological mutants are recessive. However, traits such as bristle number and body size show

little inbreeding depression (Kidwell and Kidwell, 1966; Mackay, 1985b), indicating no directional dominance on average. Estimates of proportions of additive and dominance variance from correlations among relatives also indicate most of the variation in segregating populations for these traits is additive (e.g. Clayton *et al.*, 1957). Therefore it is possible that a similar relationship between severity of homozygous effect and degree of dominance exists for mutations affecting other traits than viability.

Pleiotropy. It is well known that mutations with major morphological effects on one trait also have a multitude of pleiotropic effects on other traits (for examples in *Drosophila*, see Lindsley and Grell, 1968), including a commonly observed reduction in fitness. There are few data on the pleiotropic effects of new mutations with more subtle effects on quantitative traits. Simmons and Crow (1977) argue that mildly detrimental mutations affecting viability must have more severe pleiotropic effects on fertility, because the estimated heterozygous fitness disadvantage of mildly detrimental viability mutations is much greater than predicted on the basis of their homozygous effects and degree of dominance. For other quantitative traits, information from *Drosophila* selection lines indicates some alleles contributing to extreme values of selected traits have deleterious effects on fitness. Highly selected lines commonly contain high frequencies of homozygous inviable or infertile chromosomes with a large heterozygous effect on the selected trait (Clayton and Robertson, 1957; Frankham *et al.*, 1968; Hollingdale, 1971; Madalena and Robertson, 1975; Yoo, 1980b). However, if artificial selection is relaxed at a time when genetic variation for the selected trait still remains and natural selection only acts on the selected line, the mean phenotype generally changes little (reviewed by Falconer, 1989b), suggesting that alleles affecting the trait that segregate in natural populations are nearly neutral with respect to fitness. These observations can be reconciled if there is a correlation between the effect of the mutation on the quantitative trait and on fitness such that the more extreme the effect on the trait, the more severe the reduction in fitness. Newly arising mutations (the lethals detected in *Drosophila* selection lines may be examples) may well have large direct and pleiotropic effects, but they will not contribute to the genetic variance of the trait in an equilibrium population.

DIRECT OBSERVATIONS

Direct experimental data on the distributions of homozygous, heterozygous and pleiotropic effects of mutations affecting quantitative traits have not been available to date because of the difficulty of determining whether or not a mutation has occurred independently of its effect on the trait. If there is no observed effect on the trait, it can be because no mutations have occurred, or because the mutational effects are too small to be detected. Mutations with small effects may greatly influence the genetic variation maintained (Keightley and Hill, 1988), so it is a major challenge to design experiments capable of discerning them.

In *Drosophila*, it is possible to replicate a single stem chromosome and allow it to accumulate mutations as a heterozygote against a balancer chromosome, in an isogenic background genotype. This powerful approach was used by Mukai (1964) to accumulate mutations affecting viability, and has the advantages that mutations with recessive deleterious fitness effects are preserved, and the homozygous, heterozygous and pleiotropic effects of the mutations can be assessed sufficiently accurately to detect small effects. The problem of ascertainment of mutational events can be overcome by using transposable element mutagenesis,

because insertions of transposable elements can be detected directly by *in situ* hybridization or by restriction fragment analysis. Transposable elements cause mutations when they insert into or near coding sequences (Rubin, 1983), some of which can affect quantitative traits (Fitzpatrick and Sved, 1986; Lai and Mackay, 1990; Mackay, 1985a, 1986, 1987; Pignatelli and Mackay, 1989; Torkamanzehi *et al.*, 1988; Yukuhiro *et al.*, 1985). In the experiment described below (T.F.C. Mackay, M. S. Jackson, and R. F. Lyman, unpublished data), the *P* element mutagenesis system of Robertson *et al.* (1988) was used to create replicate, originally isogenic, *Drosophila* third chromosome lines differing only in the numbers and locations of stably intergrated *P* elements, in an otherwise isogenic background previously free of *P* elements (Mackay, 1989). The homozygous and heterozygous effects of the *P* element insertions on abdominal and sternopleural bristle score, and on viability, were assessed by comparing the means of the mutagenized lines to those of 60 *P* element free control lines extracted from the host inbred strain. The number of *P* elements in each mutagenized line was determined initially by Southern blotting, and checked by *in situ* hybridization to confirm all inserts were on the third chromosome. There were an average of 2.7 *P* element inserts per chromosome, with a range from 0–15. 94 chromosomes had at least one insert, with an average of 3.1 *P* elements among lines with at least one insert.

The data from this experiment give the first empirical information on the properties of new mutations affecting quantitative traits, although for *P* element induced mutations only.

Distributions of homozygous effects. *P* element insertions decrease homozygous viability by 32% on average – a decrease of 10.4% per *P* element insertion. 11 chromosomes were homozygous lethal (10.4%, or 3.8% per new *P* insertion). The distribution of homozygous viabilities of lines containing inserts is bimodal, with a peak at lethality and another somewhat below the mean control viability. *P* insertions have no effect on mean abdominal or sternopleural bristle score, but greatly affect the variance and higher moments of the distributions. The increment in variance among homozygous mutagenized lines compared to the control among line variance is V_m. For abdominal bristle score $V_m = 0.15V_e$ (0.05 / homozygous *P* element), and for sternopleural bristle score $V_m = 0.18V_e$ (0.06/ homozygous *P* element). V_e was estimated from the control within line variance. The distributions of effects of inserts on abdominal and sternopleural bristle scores are significantly negatively skewed ($g_1 = -1.92$ and -1.21, respectively) and are highly leptokutotic ($g_2 = 5.72$ and 11.20, respectively). Of the homozygous viable lines, 7 have effects greater than $0.7\sigma_p$ on sternopleural bristle score, and 8 have effects greater than $0.7\sigma_p$ on abdominal bristle score. These extreme lines account for over 80% of the variance of each trait. The effects of the extreme lines are for increasing and decreasing score, but the largest effects on each trait are in the direction of reducing score.

Distributions of heterozygous effects. The effects of *P* inserts heterozygous with the inbred control host strain were assessed relative to the homozygous control. Heterozygous viability is not significantly decreased relative to the control; *P* element inserts are recessive (or nearly so) with respect to viability. There is no effect of heterozygous *P* inserts on mean abdominal or sternopleural bristle score, but the variance is significantly increased. V_m due to heterozygous *P* inserts is $0.03V_e$ for abdominal and $0.01V_e$ for sternopleural bristle score. The *P* insertions with extreme bristle effects are, however, mostly recessive.

Pleiotropic effects. The highly leptokurtic distributions of mutant effects give too few degrees of freedom to test associations, but inspection of the joint effects of the deviant chromosome lines gives some idea of pleiotropy. Two of the extreme chromosome lines have effects in the same direction on both bristle traits. The effects on viability are much more pronounced – the average viability of the chromosome lines with extreme bristle effects is 0.24 relative to the control, compared to the average viability of 0.68 of all *P* insert containing lines (including lethals).

These empirical distributions of non-additive, asymmetric and highly leptokurtic mutant effects, with pleiotropic associations with other traits and fitness, point to the need to incorporate these features into theoretical predictions of the effects of new mutations affecting quantitative traits on long-term selection response, population differentiation and standing variation (e.g. Hill and Keightley, 1988; Keightley and Hill, unpublished). Identification of loci by insertional mutagenesis is also a first step towards understanding the molecular basis of quantitative genetic variation at individual quantitative trait loci- a goal which is currently within our reach.

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