

## VARIATION FROM SPONTANEOUS MUTATION FOR BODY SIZE IN THE MOUSE

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### SUMMARY

Estimates have been obtained of the variation deriving from mutation for 6-week body weight in the mouse from two experiments: (1) Long term selection was practised from an inbred base, which gave an estimate of the mutational heritability,  $h_m^2$  (the ratio of the variance from mutation each generation to the environmental variance) of 0.6%; and (2) short term selection was practised from the cross of two long separated inbred sublines, which gave an estimate of  $h_m^2$  of 0.1%. Explanations for this difference and the information it gives us about the relation between effects of mutants on body size and fitness are discussed.

### INTRODUCTION

An understanding of how variation in quantitative traits is maintained in populations and of the opportunity for long term response to selection requires knowledge of the amount of variation contributed each generation by mutation, which is the ultimate source of variation in natural and in domesticated populations. Estimates of the magnitude of the mutational variance for traits of interest and the relation between the effects of mutants on these traits and on fitness are needed in order to understand the pattern of long term selection response and to predict its rate and duration. Estimates of mutation rates to quantitative traits have been summarised by Lynch (1988). It is convenient to express this by the mutational heritability,  $h_m^2$ , the ratio of the new variance from mutation each generation to the environmental variance. Most estimates of  $h_m^2$  are for bristle number in *Drosophila*, the value being around 0.1%, but estimates for other traits and species are usually of the same order, typically somewhat smaller for species with shorter generation time and larger otherwise. The magnitude of the estimate of mutational variance is likely to be affected by the design of the experiment and the model and method used in the analysis, in particular how and whether account can be taken for the effects of natural selection. Thus variation may be removed by natural selection if mutants are deleterious with respect to fitness; and Keightley *et al.* (1993) have suggested that published estimates are substantially biased and that a more appropriate estimate of  $h_m^2$  for *Drosophila* bristle number is about 0.3%.

For mammals the only estimates have been for skeletal measurements in mice, Bailey's (1959) results giving  $h_m^2$  for tibial length of over 1.0%. It is not feasible to obtain estimates for farmed species. We have undertaken two experiments to estimate mutational variance for 6-week body weight in the mouse, a 'model' quantitative trait for experiments in mammals. In the first, long-term selection was started from an inbred base population, in the second short-term selection was commenced from a cross of two long separated inbred sublines.

### MATERIALS AND METHODS

(1) *Long-term selection from an inbred base.* High and low selection lines for 6-week body weight were founded from a C3H inbred line, which had previously been maintained by sib mating. Within family selection was practised, with 12 pairs of parents per line for the first 14 generations and 16 pairs subsequently. A circular mating design was used for the first 21 generations, subsequently about half the matings were made between full sibs and the rest at random, with the aim of increasing the chance of fixing favourable recessive genes (Caballero *et al.*, 1991). Further details and results of the first 16 and first 25 generations have been published (Keightley and Hill, 1990a, 1992). Results of 34 generations are reported here.

Estimates of mutational heritability were obtained from the regression of selection response, measured as the divergence between the high and low lines, on the selection applied, taking account of how the genetic

variance would be expected to increase as a consequence of selection with either a model of a few genes each of large effect or an infinitesimal model. Estimates were also obtained from an animal model restricted maximum likelihood (AM-REML) analysis, fitting mutational variance, litter variance, maternal environmental covariance, and random environmental variance.

(2) *Short-term selection from a cross of inbred sublines.* A cross was made between inbred sublines C57BL/6 and C57BL/10 of the highly inbred C57BL line, separated some 40 years previously and maintained by sib mating. Selection within full-sib families high and low for 6-week body weight was initiated from the F2 of the cross in a line maintained with 12 pairs and random mating, and continued for 11 generations. The additive genetic variance in the F2 was estimated from the regression of response (high-low divergence) on generation number and from AM-REML. The mutational variance and  $h_m^2$  were estimated from this variance by assuming different mutants were fixed in each line, that the between subline variance equals  $2tV_m$  for  $t$  generations, and the variance in the F2 is one-quarter of this. It was assumed that the sublines had been separated for  $t=160$  generations.

## RESULTS

(1) *Selection from inbred base.* The divergence in 6-week body weight between high and low lines is plotted in Figure 1. No control population was maintained, but there was no obvious asymmetry of response. There was little response in early generations from the inbred base; now the lines differ by about 2.5g or 1.4sd units. Estimates of  $h_m^2$  obtained by different methods were as follows: selection response assuming large gene effects 0.13%; selection response assuming the infinitesimal model (see Fig 1) 0.37%; AM-REML, global maximum at which the initial estimate of genetic variance is zero, 0.68%; AM-REML, maximum assuming  $V_{A0}=4V_m$ , 0.57%, with support interval (fall in likelihood of less than 2, which is equivalent to a 95% confidence interval) of 0.37% to 0.87%. Estimates are rather lower than those obtained earlier (Keightley and Hill, 1990a, 1992). The reasons are not known, but one possible explanation is that, with increased generations of selection, high-low divergence due to genetic change is less confounded with maternal environmental effects (Kirkpatrick and Lande, 1989).

(2) *Selection from cross of inbred sublines.* The divergence in 6-week body weight between high and low selected lines derived from the C57BL subline cross is shown in Figure 2. There were severe health problems in both these lines after generation 4, such that mean weights declined for several generations, but estimates of heritability from early generations are similar to those obtained using all the data. Estimates of the heritability in the F2 generation were 9.6% from regression of response on generation number, and 9.1% from AM-REML. These give estimates of  $h_m^2$  of 0.13% and 0.12%, respectively, i.e. approximately 0.1%, with a support interval of 0.07% to 0.2% for the REML estimate.

## DISCUSSION

The estimates of  $h_m^2$  for body weight obtained by REML for lines which were selected from the inbred C3H base are somewhat lower than those obtained by Bailey (1959) for skeletal dimensions, but much higher than obtained from selection response in these lines or by selection from the C57BL subline cross base, or from analyses of most traits in *Drosophila*. How might these results be explained? The effect of natural selection acting on mutant genes is likely to be the main factor. Thus a plausible model is that mutant effects on the metric trait of interest, in this case 6-week body weight, and fitness are sampled from a joint distribution in which mutants having a large effect on the metric trait, either increasing or decreasing, are more likely to have deleterious pleiotropic effects on fitness (Keightley and Hill, 1990b). This implies that many mutants are lost soon after they occur, and do not contribute to selection response, for example. Hence estimates of  $h_m^2$  from selection are biased downwards, as are those from other methods, but to differing extents (Keightley *et al.*, 1993). Estimates from AM-REML may incorporate most of the variance, including that subsequently lost by natural selection. It had been thought that the estimates from the cross of inbred sublines would not be greatly

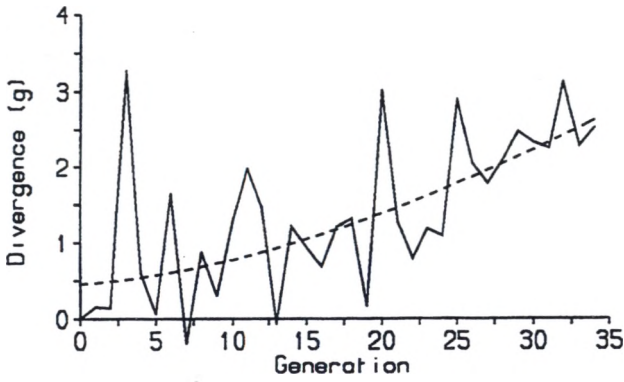


Figure 1. Divergence each generation in 6-week body weight between high and low lines selected from the C3H inbred base. The dashed line is the best fitting response assuming the infinitesimal model.

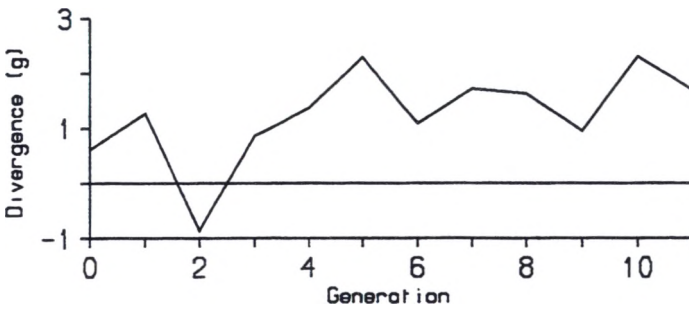


Figure 2. Divergence each generation in 6-week body weight between high and low lines selected from the C57BL/6 x C57BL/10 crossbred base, where generation 0 is the F2.

biased downwards because with full sib lines deleterious genes are fixed almost as readily as neutral genes. This may not be the case, however, in these lab maintained stocks: several families are kept each generation, with culling back to the fittest and, perhaps, phenotypically ideal family, so perhaps mutants are put at a severe selective disadvantage. Such selection might be more severe on body weight than on skeletal dimensions recorded by Bailey. Also we note that the heritability in the line cross base was about 10%, which, though smaller, is of similar order to estimates of 22% from a cross of two widely divergent inbreds, C57BL/6J and DBA/2J (S. C. Heath, P.D. Keightley and G. Bulfield, unpublished), and 37% from a mainly outbred base population (Falconer, 1973). Thus if we were to obtain an estimate of  $h_m^2$  of the order of 1% from the subline cross it would have required a base population value of heritability greater than we find in outbreds. This suggests either that the value of 0.6% is too high, or, more plausibly, that substantial natural selection operates (is operated by the breeder) in all inbred lines, and, of course, in all large populations.

It is possible, at least in principle, to obtain estimates of  $h_M^2$  from selected lines originating from an outbred base, providing selection is maintained sufficiently long that the mutation derived variance is of similar order to that initially present. In plateau populations that may lead to zero estimates, but more sophisticated analyses to distinguish artificial and natural selection effects are necessary. Under the assumption of the infinitesimal model, Beniwal *et al.* (1992) estimated  $V_M$  from selected lines and obtained negative estimates; but these are simply explained by the inappropriate nature of the infinitesimal model to predict long term response from standing variation.

Thus we conclude that the rate of generation of variation by mutation for quantitative traits such as body size in mammals is high, of the order of 0.5% per generation, but that most mutants have deleterious effects on fitness. It is not surprising, therefore, that intensely selected livestock populations show undesirable effects of one kind or another, for example leg weakness in broilers or pigs, despite unremitting selection against them.

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#### REFERENCES

- BAILEY, D.W. (1959) *J. Hered.* 50 : 26-30.
- BENIWAL, B.K., HASTINGS, I.M., THOMPSON, R. and HILL, W.G. (1992) *Heredity* 69 : 361-371.
- CABALLERO, A., KEIGHTLEY, P.D., and HILL, W.G. (1991) *Genet. Res.* 58 : 129-138.
- FALCONER, D.S. (1973) *Genet. Res.* 22 : 291-321.
- KEIGHTLEY P.D. and HILL, W.G. (1990a) *Proc. 4th World Congr. Genet. Appl. Livest. Prod.* 13 : 325-328.
- KEIGHTLEY, P.D. and HILL, W.G. (1990b) *Proc. Roy. Soc. Lond.* B242 : 95-100.
- KEIGHTLEY, P.D. and HILL, W.G. (1992) *Genetics* 131 : 693-700.
- KEIGHTLEY, P.D., MACKAY, T.F.C. and CABALLERO, A. (1993) *Proc. Roy. Soc. Lond.* B253 : 291-296.
- KIRKPATRICK, M. and LANDE, R. (1989) *Evolution* 43 : 485-503.
- LYNCH, M. (1988) *Genet. Res.* 51 : 137-148.