

ESTIMATING NEW MUTATIONAL VARIATION IN GROWTH RATE OF MICE

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SUMMARY

The amount of new genetic variation arising from mutation has important implications for long-term responses to artificial selection and for maintenance of variation in quantitative traits in natural populations. Restricted Maximum Likelihood with an Animal Model was used to estimate new mutational variance, V_M , for growth rate in the mouse from an experiment in which selection on 6 week weight was practised for 16 generations high and low from an inbred base stock. Assuming alleles affecting growth rate present in the base stock were neutral with respect to fitness, the maximum likelihood estimate of V_M as a proportion of the environmental variance, V_E , is 0.8%, and is significantly higher than zero. There is insufficient statistical power at present, however, to distinguish whether the genetic variation observed was due to mutation or was present at the start of the experiment.

INTRODUCTION

The role of new mutations in influencing long term selection response received renewed attention from Frankham (1980) who cited examples of mutations of major effect arising in selection lines. Subsequent theoretical work (Hill, 1982a, b) quantified expected responses from fixation of new mutations. An important parameter determining the expected response is the new mutational variance arising per generation, V_M , which is usually expressed as a proportion of the environmental variance, V_E (V_M/V_E = 'mutational heritability'). The only characters for which V_M/V_E is known with any precision are various *Drosophila* bristle traits, and the consensus figure from a number of studies is 0.1% (Lynch, 1988). Hill (1982b) showed that even this small increment in variance per generation can contribute substantially to response in the long term, and may do so in the short term especially if a proportion of the new variance is contributed by alleles of large effect. There is no information on mutational heritabilities, however, for traits of economic importance in animals. A number of studies involving divergence between inbred mouse sublines have provided estimates of mutational heritability for various skeletal traits (Bailey, 1959; Grewal, 1962; Festing, 1973), and these estimates are closer to 1% than the 0.1% figure quoted earlier for *Drosophila* bristles (Lynch, 1988).

This paper describes results of a continuing selection experiment which was set up in order to obtain an estimate of V_M/V_E for growth rate in the mouse. An initially inbred line of mice has been selected divergently for 16 generations. The data have been analysed by Restricted Maximum Likelihood (REML) using an Animal Model (AM). The expected increase in genetic covariance between animals due to new mutational variation as the selection experiment proceeds is taken into account, all information from covariances between relatives as well as response to selection is utilised, and random environmental effects and fixed effects can be estimated simultaneously.

MATERIAL AND METHODS

Mouse Lines. High and low lines of 12-16 pairs per generation were selected divergently for 6-week body weight using within family selection on males and females and a circular mating scheme (Kimura and Crow, 1963). The lines were established from a family of full-sibs of the C3H/HE inbred strain obtained from Bantin and Kingman Ltd. in 1986. These individuals are the parents of generation 0. The strain had been previously maintained by continued full-sib mating. The data set presently contains 1756 records.

Statistical Estimation of Mutational Variance. The statistical procedure used here is a modified version of REML as implemented by Meyer (1989). Genetic variance assumed to be present at generation 0 ($V_{g,0}$) declines because of inbreeding according to the structure of the 'Numerator Relationship Matrix' (NRM) which describes genetic covariances between all the individuals in the data set. Genetic variance is increased, however, by V_M units each generation which is allocated to each individual. Terms are added to elements of the NRM each generation to account for the increased covariance between relatives. The new mutational variation appearing in any one generation subsequently declines in the same way as that which was previously present, and the 'infinitesimal model' is assumed. In the computer program used here, the inverse of the NRM was set up according to the algorithm of Wray (1990) which includes mutation. A common environmental variance (σ_c^2) of sibs and an environmental covariance of offspring and mother (σ_{OPE}) are also included in the model.

Fixed effects of sex, generation and litter size (6 classes) were also simultaneously estimated.

RESULTS

Response to Selection. Fig. 1 shows generation averages for the high and low line, with correction for litter size (estimated by REML) applied. There is a strong effect of litter size because small mothers tend to have small litters, the members of which tend to be heavier (and vice versa). Fig. 1 shows an early response with little sign of subsequent improvement.

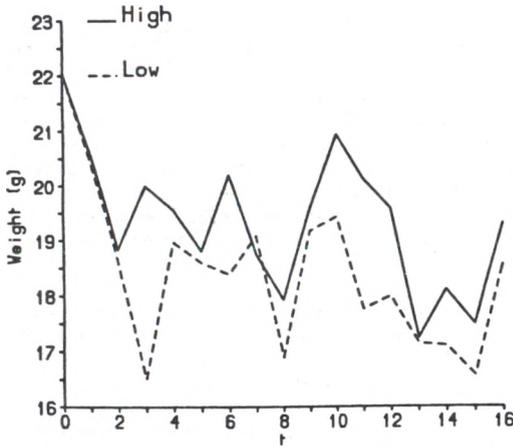


Fig. 1. Response to selection on 6 week weight in high and low lines corrected for litter size.

REML Estimate (1): Assuming Neutrality in Full-Sib Line. If it is assumed that selection is absent in the inbred line and a balance between drift and mutation has been reached, the expected genetic variance at generation 0 is $2N_e V_M$, where N_e is the effective population size. A full-sib line has effective population size $N_e \approx 2.5$, so $V_{g,0}$ is expected to be $5V_M$ for the neutral case. Constraining V_g to equal $5V_M$ and evaluating the maximum likelihood value of V_M to explain the data therefore provides an estimate of V_M/V_E for the case of neutrality in the full-sib line. Fig. 2 shows the likelihood of data with likelihood (L) expressed as $-2\text{Log}L$, as a function of V_M/V_E with ML estimates of the random environmental effects conditional on V_M/V_E . The maximum likelihood value is significantly different from $V_M/V_E = 0$ ('significance' here is taken to be $2\text{Log}L$ ratio > 3.84 which is a likelihood ratio of 6.82, and corresponds to statistical significance at the 5% level). The maximum likelihood estimate is $V_M/V_E = 0.8\%$.

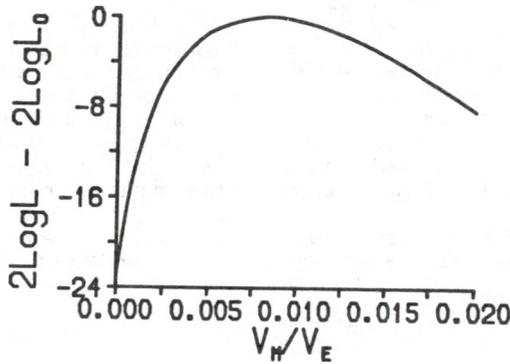


Fig. 2. Likelihood of data as function of V_M/V_E . The relationship matrix is constrained such that $V_{g,0} = 5V_M$ (neutrality in full sib line).

REML Estimate (2): Distinguishing $V_{g,0}$ from V_M . By computing the maximum likelihood value of the genetic variance for a range of values of $V_{g,0}/V_M$, it is possible to determine whether it is possible to distinguish response and variance caused by initially segregating alleles ($V_{g,0}$) from that due to mutation V_M . This is illustrated in Fig. 3. The left-hand side of the curve corresponds to explaining the data solely by mutation ($V_{g,0}/V_M = 0$) and the right-hand end solely by genetic variance initially present ($V_{g,0}/V_M \rightarrow \infty$). The latter explanation is about 3.5 times more likely than the former. The data, however, are not explainable with the model fitted without genetic variation from some source.

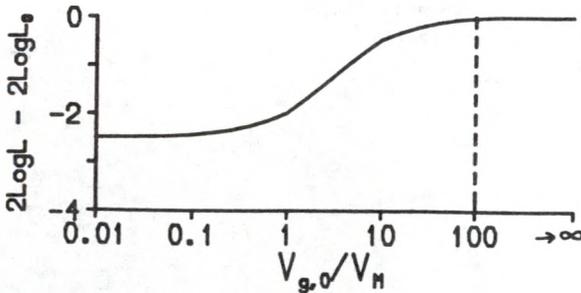


Fig. 3. Likelihood of data for models with varying proportions of initial to mutational variation.

DISCUSSION

Assuming neutrality in the full-sib line from which the selection lines were derived gives an estimate for the mutational heritability of 0.8%, which is not much different from previous estimates of mutational variation for various skeletal traits in the mouse (Lynch, 1988). The analysis shows, however, that it is not yet possible to distinguish the source of the genetic variation, i.e. whether it was there at the start of the experiment, or whether it has arisen subsequently. It is necessary to do so for the following reasons: (1) Neutrality might not hold in the full-sib line because, for example, heterozygote advantage for genes affecting body size maintains genetic variance. Theoretical evaluation of this possibility, however, makes it unlikely. (2) The genetic variance initially present is subject to much sampling variation (Lynch and Hill, 1986). (3) The model might not account for all environmental influences and the small estimate of V_g may be biased upwards.

A problem of the analysis is the use of the 'infinitesimal model' of many additive genes of small effect, which is implicit in REML and the Animal model. For analysis of 'standing variation' in a long-established population, this may be a reasonable model, but mutations are likely often to have extreme effects. This is well illustrated in the present experiment by a spontaneous recessive mutation affecting coat colour which appeared at generation 14. The mutant also reduces body size by about 10% (over 1 s.d.) and reduces viability. Since the mutant appeared in the high line, it will not become fixed or contribute much to V_M .

Acknowledgements. This work was supported by grants from the Agricultural and Food Research Council. We are grateful to Robin Thompson and Naomi Wray for advice.

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