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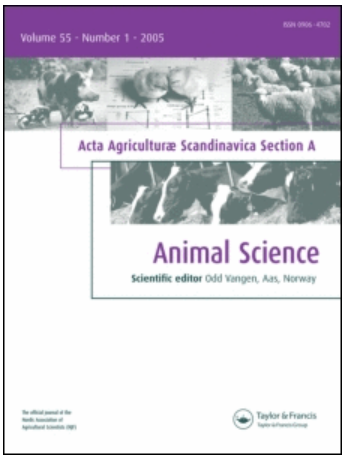

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INVITED ARTICLE

Genetically controlled environmental variance for sternopleural bristles in *Drosophila melanogaster* – an experimental test of a heterogeneous variance model

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Abstract
The objective of this study was to test the hypothesis that the environmental variance of sternopleural bristle number in *Drosophila melanogaster* is partly under genetic control. We used data from 20 inbred lines and 10 control lines to test this hypothesis. Two models were used: a standard quantitative genetics model based on the infinitesimal model, and an extension of this model. In the extended model it is assumed that each individual has its own environmental variance and that this heterogeneity of variance has a genetic component. The heterogeneous variance model was favoured by the data, indicating that the environmental variance is partly under genetic control. If this heterogeneous variance model also applies to livestock, it would be possible to select for animals with a higher uniformity of products across environmental regimes. Also for evolutionary biology the results are of interest as genes affecting the environmental variance may be important for adaptation to changing environmental conditions.

Keywords: *Drift, environmental variance, genetic variance, inbreeding, model comparisons.*

Introduction

One of the challenges in evolutionary biology and animal breeding is to understand the genetic basis of phenotypic variation and how this variation is maintained. The coefficient of variation shows stunning consistency across species (Hill et al., 2008). The question arises as to why this is the case. A straightforward suggestive answer is that there is some intrinsic mechanism maintaining variability at a certain level. Most traits show genetic variation. In fact, there are only a few examples where the mean of a trait is not heritable (e.g., Hoffmann et al., 2003; Kellerman et al., 2006). Evidence is beginning to gather that the environmental variance of a trait is also under genetic control, i.e. genes control the effect of small environmental perturbations on the variability of the trait. Different methods have been used to estimate this effect. Mackay and Lyman (2005) used chromosome-balancing techniques in *Drosophila melanogaster* to measure mean and variance of different genotypes. Rowe et al. (2006) found differences of within half-sib family variation depending on the sire. The latter approach is, however, sensitive to whether genes of large effect are segregating in some families and not in others. Therefore, it is not unmistakable evidence.

Recently a so-called heterogeneous variance model has been proposed in quantitative genetics that takes into consideration genetic effects on the environmental variance (SanCristobal-Gaudy et al., 1998). The model postulates that the environmental variance is partly under genetic control and is allowing for situations where genes affecting the mean of a trait are correlated with genes affecting the environmental variance of the trait. The model has been fitted to data by SanCristobal-Gaudy et al.

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(2001) where the aim was to evaluate the potential use of this model in selection for homogenizing the number of lambs born per litter across parities. Also, Sorensen and Waagepetersen (2003) and Ros et al. (2004) fitted a heterogeneous variance model to data on litter size in pigs and on adult weight in the snail *Helix aspersa*. Results presented in these papers all gave some support for the proposed heterogeneous variance model.

In a previous paper, we found that inbred *D. melanogaster* showed a higher environmental variance than did noninbred flies (Kristensen et al., 2005). This was an indication that the environmental variance is a parameter of the population and, therefore, partly under genetic influence.

In this study we investigated sternopleural bristle numbers in 20 inbred and 10 noninbred lines of the fruit fly *D. melanogaster*. The purposes were two-fold. First, we tested the hypothesis that the heterogeneous variance model showed the best fit to the data, indicating that there is a significant level of heritable genetic variation for environmental variance. Secondly, we investigated whether inbreeding and the rate of inbreeding affects genetic and environmental variance components.

Materials and methods

Data

A genetically diverse mass population of *D. melanogaster* was founded in August 2002 by crossing equal numbers of flies from four sets of pre-existing stocks (collected in Denmark, Australia and The Netherlands). The stocks were maintained at a high effective population size ($N > 1000$) prior to crossing. The lines used here were derived from this mass population (for details see Pedersen et al., 2005).

The lines were founded in December 2002 (eight generations after the mass population was founded). Ten lines with expected equivalent levels of inbreeding ($F \approx 0.67$) were obtained by five generations of full-sib mating (fast rate) and 10 lines by maintaining a population size of four pairs during 18 generations (slow rate) (for details see Kristensen et al., 2005 and Pedersen et al., 2005). After reaching the desired level of inbreeding, lines were flushed to sizes of approximately 500 breeding individuals. Ten noninbred control lines, each founded by approximately 500 breeding individuals, were also established and maintained parallel to the inbred lines.

Assuming that the inbreeding level of the base population from which all lines were sampled was equal to zero, the expected inbreeding coefficient (F) in a given generation (t) was calculated from the expression $F_t = (1 + 2F_{t-1} + F_{t-2})/4$ (Falconer & Mackay, 1996), for the fast-inbreeding treatment, and from the expression $F_t = F_{t-1} + (1 - 2F_{t-1} + F_{t-2})/2N_e$ (Crow & Kimura, 1970), for the slow-inbreeding treatment, assuming $N_e = 8$.

Throughout the duration of the experiment flies were maintained at standard laboratory conditions ($25 \pm 0.2^{\circ}$C, 50% RH (relative humidity), 12/12 hours light/dark cycle). Flies were sampled from the 10 lines within each treatment. A total of 200 vials with one virgin male and female were set up per line, even though later only 104 vials were used per line (each vial constituting a family). Mating and egg laying were allowed to proceed for 48 h. Thereafter, parents were removed and stored in Eppendorf tubes in a solution of ethyl alcohol and glycerol. After emergence, offspring were collected and kept under the same storage conditions as their parents.

Sternopleural bristle number was counted on both sides of the male parent and on two of its male offspring in each of 104 families. In total, sternopleural bristles were counted on 9360 flies (104 male parents + 208 male offspring from each of 10 lines per breeding regime).

Models

We analysed bristle number with two different models. The homogeneous model (HOM) is a traditional quantitative genetics model assuming an infinitesimal model. The sampling distribution of the data (vector **y** of order n, number of observations) given the parameters **b**, **p**, **a**, and V_E is the multivariate normal process [Equation (1)].

$$\mathbf{y}|\mathbf{b}, \mathbf{p}, \mathbf{a}, V_E \sim N(\mathbf{Xb} + \mathbf{Zp} + \mathbf{Za}, \mathbf{I}V_E). \quad (1)$$

The parameters are a vector of line means, **b**, a vector of permanent environmental effects for each animal with known bristle number, **p**, a vector of additive genetic values for each animal, **a**, and the variance of the conditional distribution, V_E, which is interpreted as the environmental variance. **X** and **Z** are known incidence matrices, and **I** is an identity matrix of appropriate order.

The vector **p** is assumed to follow the normal process shown in Equation (2),

$$\mathbf{p}|V_{pe} \sim N(\mathbf{0}, \mathbf{I}V_{pe}) \quad (2)$$

where V_{pe} is the variance of permanent environmental effects.

The vector **a** is assumed to follow the normal process shown in Equation (3),

$$\mathbf{a}|V_a \sim N(\mathbf{0}, \mathbf{A}V_a) \quad (3)$$

where V_a is the additive genetic variance, and **A** is the additive genetic relationship matrix.

The heterogeneous model (HET) is an extension of HOM. It allows for a genetic component of the environmental variance, which means that the environmental variance can be different for every individual [Equation (4)]:

$$\mathbf{y}|\boldsymbol{b}, \mathbf{p}, \mathbf{a}, \mathbf{b}^*, \mathbf{p}^*, \mathbf{a}^* \sim N(\mathbf{Xb} + \mathbf{Zp} + \mathbf{Za}, \mathbf{diag}(\exp(\mathbf{Xb}^* + \mathbf{Zp}^* + \mathbf{Za}^*))) \quad (4)$$

The parameters **b**, **p**, and **a** are the same as in Equation (1). **b*** is a vector of line means, **p*** is a vector of permanent environmental effects for each animal with known bristle number, and **a*** is a vector of additive genetic values for each animal. **p*** and **a*** affect the environmental variance.

The vector **p*** is assumed to follow the normal process shown in Equation (5),

$$\mathbf{p}^*|V_{pe^*} \sim N(0, \mathbf{I}V_{pe^*}) \quad (5)$$

where V_{pe^*} is the variance of permanent environmental effects.

The vectors **a** and **a*** are assumed to follow the normal process shown in Equation (6),

$$\begin{bmatrix} \mathbf{a} \\ \mathbf{a}^* \end{bmatrix} |\mathbf{G} \sim N(\mathbf{0}; \mathbf{G} \otimes \mathbf{A}) \quad (6)$$

where Equation (7) holds:

$$\mathbf{G} = \begin{bmatrix} V_a & \rho\sqrt{V_a V_{a^*}} \\ \rho\sqrt{V_a V_{a^*}} & V_{a^*} \end{bmatrix} \quad (7)$$

ρ is the genetic correlation of genes affecting the mean and genes affecting the environmental variance.

The homogeneous model was implemented using Gibbs sampling (Sorensen & Gianola, 2002), while the heterogeneous model was implemented using a combination of Gibbs sampling and a Metropolis–Hastings algorithm with Langevin–Hastings and random-walk proposals. The priors for the vectors **b** and **b*** were normal distributions with zero mean vector and very large variances. The variance parameters V_a, V_{pe}, $V_{a^\star}$, and $V_{pe^\star}$ were assigned scaled inverted chi-square distributions with four degrees of freedom and a scale parameter of 0.45; ρ was assigned a uniform prior distribution bounded between 1 and -1.

Table I. Deviance Information Criterion for the two models and the three inbreeding treatments.

	Control	Slow	Fast
HOM (1)	8643	8212	8414
HET (4)	8256	7812	7939

Results

In the comparison of the two models the heterogeneous variance model is favoured as shown in Table I. The Deviance Information Criterion is a measure of goodness-of-fit of the model accounting for model complexity, and smaller values indicate smaller deviations and therefore a better fit (Spiegelhalter et al., 2002). The criterion can only be compared within treatment, and not across treatments.

The heterogeneous variance model was used to infer parameters, as this was the favoured model. The variance of additive genetic effects affecting the environmental variance was significantly larger than zero in all three treatments (Figure 1). This implies that the size of the environmental variance has a genetic component. The additive genetic variance affecting the mean sternopleural bristle number differed between the three treatments. It was significantly ($p < 0.001$) higher in the noninbred control lines compared with the inbred lines, and also

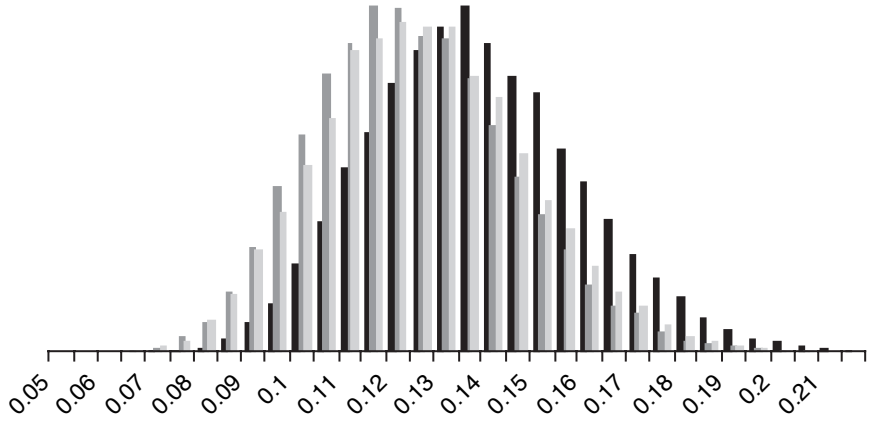

Figure 1. Marginal posterior distributions of the variance of additive genetic effects affecting the environmental variance for the three treatments fast inbreeding (light grey), slow inbreeding (dark grey), and control (black).

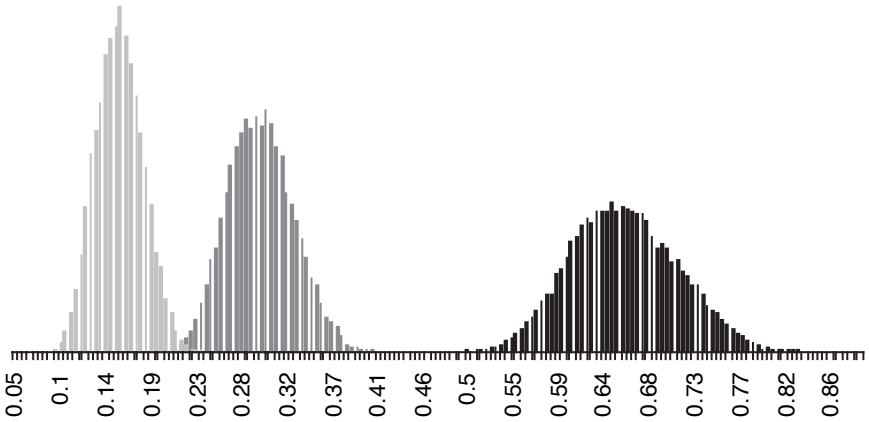

Figure 2. Marginal posterior distributions of the additive genetic variance for the three treatments fast inbreeding (light grey), slow inbreeding (dark grey), and control (black).

significantly ($p < 0.001$) higher in the slow-inbred lines compared with fast-inbred lines (Figure 2).

For both genetic variance components, the additive genetic variances in the inbred lines were expected to be 33% of the variance in the control lines, under the assumptions of neutrality and purely additive gene action. However, the variance components did not follow this expectation. The additive genetic variance affecting the mean was significantly ($p = 0.007$) higher than expected in the slow-inbred lines and significantly ($p = 0.016$) lower than expected in the fast-inbred lines. The additive genetic variance of genes affecting the environmental variance was significantly ($p < 0.001$) higher than expected in both inbred treatments.

The genetic correlation between genes affecting the mean and genes affecting the environmental variance was very high (0.91–0.94) in all lines. This means that genes conferring a high number of bristles also confer a high environmental variation in bristle number. The environmental variance did not differ significantly between lines (Figure 3); neither did the variance due to permanent environmental effects (results not shown).

Discussion

Of the two models tested in this study, the heterogeneous variance model showed the best fit. There are some differences between the two models. The first difference is that the heterogeneous variance model allows for a genetic component of the environmental variance. The second difference is that this model allows the 10 lines to have different environmental variances. It is very conceivable that the different lines have different environmental variances. However, this may be due to a genetic component. The presence of a genetic component is apparent from the fact that the model puts all evidence away from zero in the marginal posterior distribution of the variance of additive genetic effects affecting the environmental variance, i.e. there is strong evidence that this variance component is nonzero. A third difference is that the heterogeneous variance model allows for a scale effect, i.e. a relationship between the mean and the variance that is either deterministic or stochastic. In the model, this scale effect is entirely due to genetic effects.

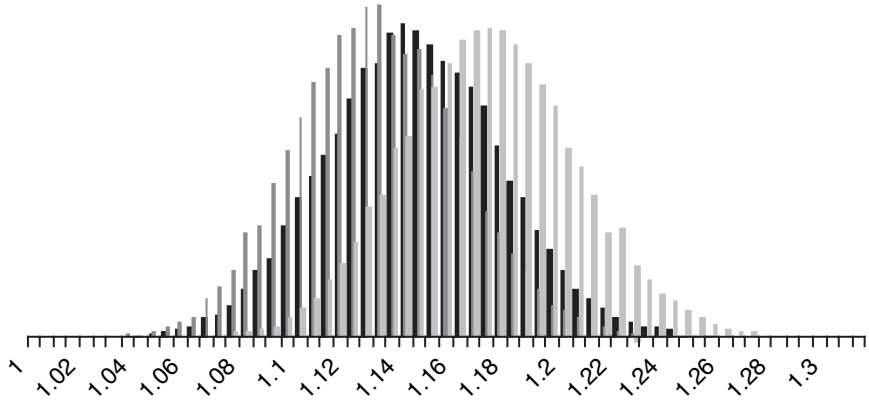

Figure 3. Marginal posterior distributions of the environmental variance for the three treatments fast inbreeding (light grey), slow inbreeding (dark grey), and control (black).

This study provides an example showing that environmental variance is a heritable trait, using bristle number in *D. melanogaster*. Other studies have reported similar results in sheep (SanCristobal-Gaudy et al., 2001), snails (Ros et al., 2004), and pigs (Sorensen & Waagepetersen, 2003) for different traits. In those studies a heterogeneous variance model postulating a genetically structured environmental variance gave a better fit compared with a traditional homogeneous variance model where all animals are assumed to have the same environmental variance. This is of great interest in animal breeding and evolutionary biology (Hill et al., 2008). In animal breeding this variation may be utilised to breed for consistency in products, and in evolutionary biology it may add to our understanding of adaptation to changing environmental conditions. So far emphasis has primarily been on understanding additive genetic effects affecting the mean. As shown here, there may be genes affecting the environmental variance. A candidate gene involved may be the heat shock protein Hsp90. When expression of Hsp90 is inhibited cryptic genetic variation has been shown to be expressed and the phenotypic variation increased (Rutherford & Lindquist, 1998). Hsp90 may therefore constitute a buffer mechanism important for regulating the level of phenotypic variation. However, more studies utilizing novel techniques in systems biology combined with quantitative genetic methods are needed to gain information on specific genes affecting the environmental variance.

To our knowledge this is the first study that investigates the consequences of inbreeding on variability using a heterogeneous variance model. The additive genetic variance of genes affecting environmental variance did not decrease with inbreeding, as expected for a trait assumed to be neutral and mainly governed by additive gene action. Environmental variance has been hypothesised to be maintained at equilibrium between engineering costs and the benefit of keeping performance stable (Hill et al., 2008). Therefore, variability is likely to have fitness implications and is thus expected to be highly influenced by nonadditive genetic effects. This might explain the non-neutral and/or nonadditive behaviour of the genetic variance with inbreeding.

We found a significant decrease in additive genetic variance with inbreeding and more so with fast inbreeding (Figure 2). The results are qualitatively similar to the results on effect of inbreeding on genetic variance presented in Kristensen et al. (2005) that used data from the same experiment. Gilligan et al. (2005) found that both fast and slow inbred lines showed more genetic variation than expected for both abdominal and sternopleural bristle number in *D. melanogaster*. However, in both these studies, there was a large variation around the mean, with some lines having more variation than the non-inbred lines. This variation between lines is a fundamental feature of the drift process.

Our study shows that genes conferring a high number of bristles also confer a high variability in bristle number, because the genetic correlation was close to unity. This is a well known scale effect. However, here it has a genetic interpretation. A selection experiment could be set up to prove this scale effect without being dependent on the statistical model used.

The environmental variance was not significantly affected by inbreeding, which is in contrast with our earlier findings (Kristensen et al., 2005). The reason for this discrepancy is unknown, but based on the new results obtained using a more sophisticated model to analyse the data we could not find evidence for inbreeding depression for canalisation, which has been suggested by Fowler and Whitlock (1999).

This study gives statistical support to the conjecture that there are genes controlling the environmental variance. This could be a result of genetic control of the stability of development. Developmental instability can be measured by fluctuating asymmetry. Since sternopleural bristle number of the flies was counted on both sides in this study, an analysis of asymmetry should be possible, and might show genetic variation for fluctuating asymmetry.

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