

Does a global robustness exist? Relationship between traits following genetic heteroscedastic models: Litter size and Birth weight in mice

L. Bodin¹, I. Cervantes², J.P. Gutiérrez² & N. Formoso-Rafferty²

¹GenPhySE, INRA, 31320 Castanet-Tolosan, France

²Universidad Complutense de Madrid, Facultad de Veterinaria, Departamento de Producción Animal, Spain

Loys.Bodin@inra.fr (Corresponding Author)

Summary

Improving robustness of animals has become a real challenge for most of animal productions. However, the existence of a global robustness, common to several traits submitted each to changes of different variation factors, is still questionable. Analysis of genetic parameters for the mean (location) and the variability (dispersion) of litter size jointly with those of birth weight have been made on data from a mice selection experiment. A DHGLM procedure implemented in the ASReml software and adapted for a bivariate analysis was run to estimate the variances and covariances of the genetic components for the location and the dispersion of these traits. The strong negative genetic correlations between LS location and dispersion as well as between LS location and BW dispersion confirmed the previous results. The genetic correlation between the LS dispersion and BW dispersion was low ($r_g=0.29$; $SE=0.15$) and provided us with a partial and preliminary answer about a global robustness.

Keywords: robustness, environmental variability, bivariate, litter size, birth weight, mouse

Introduction

The global robustness of animals for production traits, which can be defined as their genetic ability to perform homogenous productions under different environmental conditions, is a strategic issue for animal breeders. Although several methods to estimate the larger or lower genetic sensitivity of animals to express a specific trait in various environments have been developed, these methods were never applied to several traits together and the existence of a global robustness is still questionable. To what extent can we consider a global robustness or a specific robustness for each trait under specific environmental variations? The present paper is aimed to provide some clues to this question through the analysis of the correlation between the genetic effects which control the environmental variability of two mice traits. Results of a bivariate heteroscedastic model which permitted obtaining genetic values for the mean and the dispersion of each trait as well as all the variance-covariance parameters for these components are hereby presented.

Material and methods

Data from 16 generations of a successful divergent selection experiment designed for environmental variability of birth weight were used (Formoso-Rafferty *et al.*, 2016a).

At each generation and for each line, a total of 43 males and 43 females offspring from the 10 mothers with the highest and lowest predicted genetic value for birth weight residual variability, were selected to generate the following generation of the high (Hvar) and low (Lvar) variability lines. This procedure was improved by

implementing the weighted selection, allowing more descendants from the best mothers if the mean co-ancestry was not increased. A simulated annealing algorithm (Fernández & Toro, 1999) was used to reach the optimal solution. Individual inbreeding coefficients were controlled also by avoiding mating between animals sharing grandparents. More details of the selecting process can be found in Formoso-Rafferty *et al.* (2016a).

The data gathered information about 2235 litters of 1350 females of the 17 selection generations of the High and Low variability lines. The litter size (LS) at birth varied from 1 to 17 and was on average 9.30 pups per litter ($\sigma=2.94$), while the individual birth weight (BW) of the 23125 recorded pups were on average 1.56g ($\sigma=0.22$). In order to obtain means and variance of similar order for both variables, the individual BW were multiplied by 10 and then expressed in decigrams. As in Formoso-Rafferty *et al.* (2016a) birth weight of the progeny were assigned to the dam and considered as repetitions of a dam trait. Direct and indirect selection results and trends observed during the 7 first selection generations were published in details in Formoso-Rafferty *et al.* (2016a, b).

Model

A bivariate homoscedastic animal model was firstly fitted on LS and BW to check the data and to provide a first estimation of the genetic parameters. Secondly, a bivariate heteroscedastic model was fitted. The model followed that developed by SanCristobal-Gaudy *et al.* (1998) which assumes that the environmental variance of a trait T is heterogeneous and partially under genetic control. The general univariate expression of

the model is:
$$y_T = \mu_T + u_T + \exp\left(\frac{\eta_T + v_T}{2}\right) \varepsilon_T$$
, where μ_T and η_T represents the fixed and random non-genetic effects affecting the mean (location parameter) and the environmental variability (dispersion parameter) of the trait, respectively; u_T and v_T are the random additive genetic effects for the location and the dispersion of the trait respectively; and ε_T is a random term following a standardized normal distribution. This heteroscedastic model has been implemented in ASReml 4 (Gilmour *et al.*, 2014) following the double hierarchical generalized linear model specifications developed by Felleki *et al.* (2012); therefore all calculations were made using this software. The bivariate modelling used in the present study, deals with the structure difference between the design of both traits: about nine BW data for each LS record and considers jointly two traits ($T=\{L,B\}$), each following a heteroscedastic model with genetic and non-genetic effects affecting the location and the dispersion parameters of the considered traits. Moreover, this bivariate modeling takes into account the covariances between all the trait components, and permits to estimate the genetic correlations between i) the location parameter of the two traits (corresponding to the genetic correlation estimated in the bivariate homoscedastic model), ii) the dispersion parameters of the two traits, iii) the location of each trait with the dispersion of the alternate trait. Fixed and random effects which were included in each model for each trait are displayed in Table 1. Breeding values (EBV) for the location and dispersion of LS (u_L and v_L) and BW (u_B and v_B) were averaged within generation and line.

Results and discussion

The genetic variances for LS and BW, as well as the heritabilities and genetic

correlation, estimated with a classical homoscedastic bivariate model (Table 2) were in full agreement with (Formoso-Rafferty *et al.*, 2016b) and the genetic correlation between these traits was null ($rg_{(uL,uB)}=0.004$; $SE=0.10$).

Table 1. Fixed and random effects included in each sub-model (location and dispersion) for the litter size (LS) and birth weight (BW) traits.

		Litter size (LS)		Birth weight (BW)	
		location	dispersion	location	dispersion
Fixed effects	Parity	x	x	x	x
	Litter size			x	x
	Sex			x	x
Random effects	Litter			x	x
	Dam	u_l	v_l	u_B	v_b

The mean breeding values for dispersion component of BW per generation and line obtained by the bivariate heteroscedastic model are displayed in Figure 1. as already reported (Formoso-Rafferty *et al.*, 2016a), this divergent selection was highly successful. Indeed the difference of EBV for BW variability between lines still increased since the 7th generation when they were reported. At the last generation this EBV difference ($\Delta=1.08$) was 8.8 times the standard deviation of the EBV at the first generation.

Table 2. Genetic (u) variance components for Litter size (LS) and Birth weight (BW) estimated with a homoscedastic model, and resulting heritabilities (h^2) and genetic correlations (rg); (standard errors in brackets).

	Var-Cov u		h^2 - rg	
LS	1.89 (0.33)	0.00 (0.11)	0.08 (0.01)	0.00 (0.10)
BW		0.68 (0.09)		0.47 (0.08)

Figure 1. Average EBV per line and generation for the dispersion component of BW over the 16 selection generations (standard deviation in brackets).

Results of the bivariate heteroscedastic modeling (Table 3) showed that for LS the genetic variances of the location parameters were lower than the genetic variances obtained with the classical homoscedastic model (0.98 versus 1.89), while it was not the case for BW. The genetic variance for LS dispersion is larger than similar estimations found in the literature. This high value could be due to the fact that the high and low lines were analyzed together or by the lack of an important factor in the model. We have checked that considering generation and line effects in the location and dispersion sub-models, notably decreased the genetic variance for the location, but did not change very much the genetic variance for the dispersion and the genetic correlation between these parameters. In our data set it was not possible to separate the permanent environmental and the genetic effects since there were few litters per animals (1.40 in average). It is possible that it introduced some bias leading to an overestimation of the genetic correlation. However, analysis of pig LS with similar heteroscedastic models

showed that even when all sows had at least 5 litters, and when a permanent environmental effect could be fitted ($s^2p=0.97$), both genetic variances for the mean and for the variability of LS ($s^2u=1.99$; $s^2v=0.189$) were relatively high and the genetic correlation between location and dispersion was also negative ($rg=-0.42$) and in the same range as in the present study.

It should be noted however that the impact of the genetic heterogeneity on the total phenotypic standard deviation is much higher for LS than for BW. Indeed the ratio of standard deviation of performances for genetically extreme animals for their variability ($\sigma_{max}/\sigma_{min} = e^{(2\sigma_v)}$) was 3.50 for LS and only 1.50 for BW; however this relatively lower genetic variability for BW dispersion permitted a real genetic progress of BW variability in these lines (Figure 1 and Formoso-Rafferty *et al.* (2016a)).

Table 3. Variances and correlations between the genetic effects of the location (*u*) and dispersion (*v*) components of Litter size (LS) and Birth weight (BW) estimated with the heteroscedastic model (standard errors in brackets).

		LS				BW			
		<i>u_L</i>		<i>v_L</i>		<i>u_B</i>		<i>v_B</i>	
LS	<i>u_L</i>	0.98	(0.18)	-0.63	(0.01)	0.18	(0.10)	-0.54	(0.13)
	<i>v_L</i>			0.41	(0.07)	0.22	(0.09)	0.29	(0.15)
BW	<i>u_B</i>					0.65	(0.08)	0.32	(0.13)
	<i>v_B</i>							0.04	(0.01)

The genetic correlation between the location and dispersion parameters of LS was high and negative ($rg_{(u,v)L} = -0.63$; $SE=0.01$). In contrast the correlation between these parameters was moderate and positive for BW ($rg_{(u,v)B} = 0.32$; $SE=0.13$). Both results fully agree with the previous estimations made on the 7 first selection generations (Formoso-Rafferty *et al.* 2016a, b). Most importantly, this bivariate heteroscedastic model permitted to estimate all the genetic correlations between location and dispersion components not only within but also between traits. Thus, the genetic correlation between the location parameters of LS and BW was low ($rg_{(uL,uB)} = 0.18$; $SE=0.10$). Its probability to be close to zero was consistent with the very low value estimated with the homoscedastic model.

The high negative correlation between the mean level of LS and the dispersion component of BW ($rg_{(uL,vB)} = -0.54$; $SE=0.13$) agreed with the phenotypic observations made during the selection process and the indirect response estimated until the 7th generation (Formoso-Rafferty *et al.* (2016b)). Moreover, the phenotypic relationship between LS and BW variability could be partially explained by the relationship between the foetal or embryonic losses from ovulation to parturition and the BW variability. When these losses decrease, the BW variability decrease (Mesa *et al.*, 2006, Gardner *et al.* 2007), and when these losses decreases, if there is no change of ovulation rate, then the LS at birth also decrease. However that does not explain the genetic relationship between mean LS and BW variability which comes from the expression of genes in common.

In contrast, the genetic correlation between the dispersion parameters of both traits was positive ($rg_{(vL,vB)} = 0.29$; $SE=0.15$). This suggested that the least sensitive animals to micro-environmental variations for expressing one trait tended to be also slightly less sensitive for the expression of the other trait. However the joint distribution of breeding values for variability of LS (V_{LS}) and BW (V_{BW}) of animals of the 5 last generations (Figure 2) clearly showed that although the difference between lines were

highly significant for V_{BW} ($\Delta=0.96$; $P<0.001$) and V_{LS} ($\Delta=0.32$; $P<0.001$), there was no doubt that the indirect response in LS variability was much lower than the direct response in BW variability. This low, although significant, correlation also means that if, to some extent, a global robustness might exist, it is relatively low in comparison to the specific robustness which led to the high genetic progress obtained by selection (Figure 1).

Figure 2. Breeding values for the dispersion (V_{LS}) or location (μ_{LS}) component of LS according to the breeding values for the dispersion of BW (V_{BW}), for animals of the 5 last selection generations marked per line.

Conclusions

The divergent selection on variability of BW was highly successful and led to a large difference of BW between lines. The high negative genetic correlation between BW variability and LS level confirmed the trends already observed. The low positive genetic correlation between variability components of both traits might argue in favour of a low global robustness.

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