

# Estimation of direct and maternal genetic correlation of Birth Weight with its environmental maternal variability in mice

N. Formoso-Rafferty<sup>1</sup>, I. Cervantes<sup>1</sup>, J.P. Gutiérrez<sup>1</sup>, L. Bodin<sup>2</sup>

<sup>1</sup>Universidad Complutense de Madrid, Facultad de Veterinaria, Departamento de Producción Animal, Spain

<sup>2</sup>INRA, GenPhySE, Castanet-Tolosan, France  
gutgar@vet.ucm.es (Corresponding Author)

## Summary

In polytocous species like pig, rabbit and mice, environmental variability of birth weight (BW) is generally studied assigning each BW record of a litter to the dam and considering that all genetic effects are maternal. However a direct effect might exist and could induce bias in the parameter estimations. In this paper, analyses of genetic parameters for the mean (location) and the variability (dispersion) of BW has been made on mice data from a divergently selection experiment on BW considering maternal genetic effects on the location and on the dispersion of BW together with a direct genetic effect on its location. They were done through a DHGLM procedure implemented in the ASReml software which could deal with both direct and maternal effects and which provided their variances and covariances for the location and the dispersion. The correlation between maternal genetic effects for the BW location and the BW dispersion was positive and confirmed results previously obtained. The new genetic correlation between a direct genetic effect on the location and the maternal genetic effect on the dispersion of BW was also positive. Thus increasing the individual BW, whatever the direct or maternal component concerned by the selection, should be avoided if BW variability is ignored.

*Keywords: robustness, environmental variability, maternal effect, birth weight*

## Introduction

In most of studies about environmental variability of birth weight (BW) (Damgard *et al.*, 2003; Garreau *et al.*, 2008; Bodin *et al.*, 2010; Canario *et al.*, 2010; Formoso-Rafferty *et al.*, 2016a), individual records were assigned to the dam and considered as repetitions of a dam trait. These different measures of the trait permitted to estimate the genetic component of the environmental variance with a good accuracy, but could be biased or incorrectly estimated if direct genetic effects were strong. Moreover, genetic correlation between direct effect on BW mean and that maternal environmental variability has always been ignored and could have a relevant value that would lead to undesirable evolution of the BW mean if selection was implemented on variability ignoring that genetic correlation. Although the indirect selection response in individual BW has been observed during selection experiment on BW variability in rabbit (Garreau *et al.*, 2008) and in mice (Formoso-Rafferty *et al.*, 2016b), correlations between direct and maternal components of the BW mean with those of the BW variability has never been estimated due to the lack of software available. The aim of this paper was to estimate these parameters from data of a divergent selection experiment on environmental variability of BW in mice (Formoso-Rafferty *et al.*, 2016a).

## Material and methods

Data from 16 generations of a successful divergently selection experiment designed for environmental variability of BW in mice were used (Formoso-Rafferty *et al.*, 2016a).

At each generation and for each line, a total of 43 males and 43 females offspring of the 10 mothers with the highest and lowest predicted genetic value for BW residual variability, were selected to generate the following generation of the high and low variability lines. This procedure was improved by implementing the weighted selection, allowing more descendants from the best mothers if the 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 of 2235 litters of 1350 females recorded since the beginning of the experiment. The individual BW of the 23125 recorded pups were on average 15.60g ( $\sigma=2.25$ g).

## Model

The heteroscedastic model developed by SanCristobal-Gaudy *et al.* (1998) which assumes that the environmental variance of a trait is heterogeneous and partially under genetic control, were used. In the present study the general expression of this model is:

$$y = \mu + u + m + l + \exp\left(\frac{\eta + m^* + l^*}{2}\right) \epsilon$$
, where  $\mu$  and  $\eta$  represent the fixed effects affecting the mean (location parameter) and the environmental variability (dispersion parameter) of the trait,  $l$  and  $l^*$  are the litter effects: random non-genetic effects affecting respectively the location and the dispersion of the trait;  $m$  and  $m^*$  are the maternal genetic effects affecting the location and the dispersion of the trait;  $\epsilon$  is a random term following a standardized normal distribution and  $u$  is the direct genetic effect affecting the location of the trait. This last term was not considered in previous studies (Formoso-Rafferty *et al.*, 2016a) and could therefore introduce bias.

The general variance structure of this modelling is:

$$Var \begin{pmatrix} u \\ m \\ m^* \end{pmatrix} = \begin{pmatrix} \sigma_u^2 & \rho_{um}\sigma_u\sigma_m & \rho_{um^*}\sigma_u\sigma_{m^*} \\ \rho_{um}\sigma_u\sigma_m & \sigma_m^2 & \rho_{mm^*}\sigma_m\sigma_{m^*} \\ \rho_{um^*}\sigma_u\sigma_{m^*} & \rho_{mm^*}\sigma_m\sigma_{m^*} & \sigma_{m^*}^2 \end{pmatrix} \otimes \mathbf{A}$$

This heteroscedastic model has been implemented in ASReml4 (Gilmour *et al.*, 2014) following the double hierarchical generalized linear model specifications developed by Felleki *et al.* (2012). It can also handle a genetic structure across genetic effects (i.e. considering direct and maternal genetic effects) and permits to estimate the genetic variances and covariances of these effects for the location and the dispersion of the trait.

However due to convergence issues all parameters could not be estimated all at once and three models, including the genetic effects two by two, were successively run. Genetic variance-covariances which were estimated in each model are shown in Table 1.

Table 1. Genetic effects and genetic variances and covariances parameters estimated two by two in each 3 models.

Model	Genetic effects		Variances		Covariances
MI	$u$	$m$	$\sigma_u^2$	$\sigma_m^2$	$\rho_{um}\sigma_u\sigma_m$
MII	$m$	$m^*$	$\sigma_m^2$	$\sigma_{m^*}^2$	$\rho_{mm^*}\sigma_m\sigma_{m^*}$
MIII	$u$	$m^*$	$\sigma_u^2$	$\sigma_{m^*}^2$	$\rho_{um^*}\sigma_u\sigma_{m^*}$

Note that model MI corresponds to a classical direct-maternal homoscedastic model, while the two others are heteroscedastic models, including a genetic effect on the location and another on the dispersion of individual BW.

All models included the same fixed effects: parity number of the dam, litter size at birth and sex for the location and the dispersion.

## Results and discussion

Fitting direct and maternal genetic effects for the trait and its environmental variability was not possible under the free available software used to compute breeding values during the selection experiment (Ibáñez-Escriche *et al.*, 2008) and to analyse the direct and indirect responses (Pun *et al.*, 2013; Formoso-Rafferty *et al.*, 2016ab). Moreover, reliable results were not possible to be obtained for the whole model through the ASReml 4.1 software, probably due to the high complexity of the model that implies working on the residual variability and estimating simultaneously three different genetic correlations. However, splitting the full model in 3 allowed estimating all the parameters, nevertheless not all at once, but in return it provided two estimates for each variance. These whole parameters are displayed in Table 2.

Table 2. Variances (diagonal) and genetic correlations (above diagonals) for direct ( $u$ ) and maternal ( $m$ ) effects affecting the BW mean, and maternal effect affecting the residual variability ( $m^*$ ) assessed from a homoscedastic model (I) or from heteroscedastic models, either considering the maternal genetic effect on mean BW (II), or the direct genetic effect (III) (standard errors in brackets).

	Direct BW ( $u$ )	Maternal BW ( $m$ )	Maternal Var (BW) ( $m^*$ )
Direct BW ( $u$ )	I: 0.52 (0.13) III: 0.10 (0.02)	I: -0.03 (0.18)	III: 0.64 (0.24)
Maternal BW ( $m$ )		I: 0.41 (0.10) II: 0.62 (0.10)	II: 0.26 (0.13)
Maternal Var(BW) ( $m^*$ )			II: 0.04 (0.01) III: 0.03 (0.01)

The variances of the direct and maternal effects on the mean BW were in the same order of magnitude in models MII and MIII (**MII:  $\sigma_m^2 = 0.52$ , SE=0.13**; **MIII:  $\sigma_m^2 = 0.41$ , SE=0.10**; **MIII:  $\sigma_m^2 = 0.62$ , SE=0.08**) and led to similar heritabilities ( $h^2_u=0.13$ ;  $h^2_m=0.10$ ) in agreement with previous results got on the first selection generations of this experiment (Ibáñez-Escriche *et al.*, 2008; Pun *et al.*, 2013; Formoso-Rafferty *et al.*, 2016a). The genetic correlation between direct and maternal effects was nil ( **$r_g(u, m) = -0.03$ , SE=0.18**).

The variance of the direct genetic effect on the location estimated through the model MIII ( $\sigma_u^2 = 0.10$ ,  $SE=0.02$ ), for its part, is much lower than in the homoscedastic model MI, perhaps because the genetic variability of BW within litter, corresponding to the maternal effect on the dispersion, is highly confounded with the genetic individual variability of BW which represents the direct genetic effect.

The variance of the maternal effect on the BW dispersion was low and similar in model MII and MIII ( $MII: \sigma_{\sigma}^2 = 0.04$ ,  $SE=0.01$ ;  $MIII: \sigma_{\sigma}^2 = 0.03$ ,  $SE=0.01$ ). This value led to a ratio of 1.5 for the standard deviation of performances of genetically extreme dams for the BW variability of their offspring ( $\sigma_{\text{max}}/\sigma_{\text{min}} = e^{(2\sigma)}$ ), and confirmed the results already obtained on these divergent lines (Pun *et al.*, 2013; Formoso-Rafferty *et al.*, 2016a).

The genetic correlation between maternal effect on BW mean and BW dispersion was positive ( $r_g(m, m^*) = 0.26$ ;  $SE=0.13$ ) and close to estimations obtained by a Bayesian method (Pun *et al.*, 2013; Formoso-Rafferty *et al.*, 2016a) on the 7 first selection generations. Furthermore, the genetic correlation between the maternal genetic effect on the dispersion and the direct genetic effect on the location was also positive ( $r_g(u, m^*) = 0.64$ ;  $SE=0.24$ ) and considerably higher. Thus both genetic correlations between the maternal effect for the dispersion and either the maternal ( $r_g(m, m^*)$ ) or the direct ( $r_g(u, m^*)$ ) effect for the location was significantly positive. It means that selecting for decreasing the variability of BW would decrease the mean BW of the animals (correlation with the direct effect) but also would decrease the maternal ability (correlation with maternal effect). Moreover, as homogeneity has been addressed as related to productivity and animal welfare, selecting to increase BW ignoring changes in variability would be dissuaded. However due to difficulties to estimate some parameters, these results need to be verified on additional data.

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