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Correlated genetic trends for production and welfare traits in a mouse population divergently selected for birth weight environmental variability

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The objective of this work was to study the changes that, selecting for environmental variability of birth weight (BW), could bring to other interesting traits in livestock such as: survivability at weaning (SW), litter size (LS) and weaning weight (WW), their variability assessed from standard deviations of LS, standard deviation of WW (SDWW) and also the total litter weight at birth (TLBW) and total litter weight at weaning. Data were registered after eight generations of a divergent selection experiment for BW environmental variability in mice. Genetic parameters and phenotypic and genetic evolution were assessed using linear homoscedastic and heteroscedastic models in which the traits were attributed to the female, except BW and WW that were in some models also attributed to the pup. Genetic correlation between the trait and variability levels was −0.81 for LS and −0.33 for WW. Clear divergent phenotypic trends were observed between lines for LS, WW and SDWW. Although animals were heavier in the high line, TLBW and at weaning was greater in the low line. Despite the negative genetic correlation that was obtained, SDWW was also higher in the high line. Heritabilities were 0.21 and 0.06, respectively, for LS and SW. Both phenotypic and genetic trends showed clear superiority of the low line over the high line for these traits, but inferior for WW. Heteroscedastic model performed similar to the homoscedastic model when there was enough information. Considering LS and survival, the low line was preferred from a welfare point of view, but its superiority from the productivity perspective was not clear. Robustness seemed higher as shown by a low variation and having a benefit to the animal welfare, but this still remains unclear. It was concluded that low variation benefits the welfare of animals.

Keywords: canalisation, robustness, genetic trends, mice

Implications

Genetic selection to decrease environmental variability of birth weight (BW) improves robustness in the sense of achieving higher survivability and litter size (LS) in mice. This will probably be the same in prolific livestock species like pigs or rabbits. Selecting directly on standard deviation could be possible to achieve.

Introduction

The homogeneity of traits in animals, and particularly homogeneity of body weight, has become important in recent years (Moreno *et al.*, 2011). Several studies have shown evidence of heterogeneity in the residual variance in different livestock species (Högberg and Rydhmer, 2000; Jaffrezic *et al.*, 2000), and statistical evidence of genetic control of trait homogeneity for farm animals has also been demonstrated (Hill and Mulder, 2010). In addition, selecting for modifying the environmental variability in mammals has been shown to be possible in selection experiments in rabbits (Garreau *et al.*, 2008) and mice (Formoso-Rafferty *et al.*, 2015). Rabbits and mice were chosen as experimental mammals in selection experiments because of their short generation interval and any conclusions based on these populations can easily be extrapolated to other livestock (Hill and Caballero, 2000).

Divergent selection experiments are useful to examine the feasibility of selecting traits of interest. Direct and correlated responses can be studied by comparing the means of high and low lines for traits of interest and for different traits after selection (Zomeño *et al.*, 2013).

Recently, Formoso-Rafferty *et al.* (2015) reported a successful divergent selection experiment in mice for environmental

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variability of BW. This success in modifying environmental variability for BW could be accompanied by changes in other interesting productive traits (Moreno *et al.*, 2011). Within this context some authors had previously reported relationships between homogeneity in weight and important traits such as fertility or LS (Bolet *et al.*, 2007; Larzul *et al.*, 2014), and robustness traits such as welfare (Mormede and Terenina, 2012) or survival (Högberg and Rydhmer, 2000; Damgaard *et al.*, 2003; Garreau *et al.*, 2008). Therefore, before implementing the environmental variability of BW as a target trait in a breeding scheme, knowledge about the impact of this kind of selection in other traits would be needed.

The objective of this work was to study the changes that selecting for environmental variability can bring to other interesting traits in livestock such as survivability, LS and weaning weight (WW).

Material and methods

Data

Data proceeded from the successful divergent selection experiment conducted to modify the environmental variability of BW by Formoso-Rafferty *et al.* (2015). The experiment started from a created mouse population originating from a balanced genetic contribution of three inbred mice lines: BALB/c, C57BL and CBA. The three-way cross-population was previously maintained in panmixia during 40 generations ensuring high levels of both genetic and phenotypic variability. This high-variability population was also the origin for other selection experiments (Fernández *et al.*, 1998; Gutiérrez *et al.*, 2006; Ibáñez-Escriche *et al.*, 2008; Moreno *et al.*, 2011; Pun *et al.*, 2013). To set up the low and high-variability lines, initially a total of 64 males and females were randomly mated one male to one female having two litters in order to evaluate the mothers for the environmental BW variability of their offspring. A total of 43 male and female offsprings from ten mothers with the highest and lowest predicted genetic value for BW environmental variability were selected to establish the first generation of the high and low-variability lines. This process was followed within line over seven additional generations. This procedure was improved by implementing weighted selection by allowing more descendants from the best litters if mean coancestry was not increased. A simulated annealing (Formoso-Rafferty *et al.*, 2015) was used to reach the optimal solution. Individual inbreeding coefficients were controlled by avoiding mating between animals sharing grandparents. More details of the selecting process can be found in Formoso-Rafferty *et al.* (2015).

LS and survivability at weaning (SW) for each parturition were recorded across the experiment. Individual BW and WW was also recorded across generations. Phenotypic standard deviations of LS (SDLS) within female, and standard deviations WW (SDWW) within litter, were also considered as traits and afterwards analysed. Note that only two records of LS were used to calculate SDLS when available, and that single litters of the same female were used to analyse LS, but removed to analyse SDLS. Finally, total litter weight at birth (TLBW) and total litter weight at weaning (TLWW) were also registered to simultaneously account for, in a unique integrated trait, LS and BW in the TLBW and LS, WW and SW in the TLWW. The mean of the traits and number of records are shown in Table 1. The pedigree file contained 12 637 records including five generations of the panmictic population.

Models

Three different models were used to analyse the traits. First, a classical homoscedastic model (Model HO_m) was used to estimate variance components and to predict breeding values for LS, SW, WW, SDLS, SDWW, TLBW and TLWW with the following equation:

$$y_i = \mathbf{x}_i\mathbf{b} + \mathbf{w}_i\mathbf{m} + \mathbf{v}_i\mathbf{c} + \mathbf{e}$$

where y_i is either LS, SW, WW, SDLS, SDWW, TLBW or TLWW of the individual i, $\mathbf{b}$ the vectors of the systematic effects; $\mathbf{m}$ the vector of the direct genetic effect of the female (the mother when the record belongs to the pup) and $\mathbf{c}$ (not fitted for SDLS) the vector for the permanent environmental effect (litter effect for WW); $\mathbf{x}_i$, $\mathbf{w}_i$ and $\mathbf{v}_i$ are the incidence vectors for systematic, animal and permanent effects, respectively. The genetic effect $\mathbf{m}$ is Gaussian with $\mathbf{m} \sim N(\mathbf{0}, \mathbf{A}\sigma^2_m)$, where $\mathbf{A}$ is the additive genetic relationship matrix and σ^2_m is the additive genetic variance of the female effect, the vector $\mathbf{c}$ is assumed to be independent, with $\mathbf{c} \sim N(\mathbf{0}, \mathbf{I}_c\sigma^2_c)$ where $\mathbf{I}_c$ is the identity matrix of equal order to the number of mothers and σ^2_c is the permanent environmental variance, and the vector $\mathbf{e}$ is assumed to be independent, with $\mathbf{e} \sim N(0, \mathbf{I}\sigma^2_e)$, and σ^2_e is the residual variance. The fitted systematic effects were the same across models and are described below.

The second model was a homoscedastic direct-maternal animal model (Model HO_i) that was used to analyse BW and WW:

$$y_i = \mathbf{x}_i\mathbf{b} + \mathbf{w}_i\mathbf{m} + \mathbf{v}_i\mathbf{c} + \mathbf{e}$$

with all the model definitions as the previous model, but $\mathbf{a}$ being the vector of the direct genetic effect of the pup and

Table 1 *Number of records, animals in the pedigree, dams, litters and mean and standard deviation for eight analysed traits*

Traits	Records	Animals	Dams	Litters	Mean ± SD
LS	1266	11 393	721	1266	9.72 ± 2.92
SW	1266	11 393	722	1266	85.29 ± 21.73
BW	12 051	12 637	1265	1265	1.57 ± 0.21
WW	10 587	12 637	712	1232	11.28 ± 2.25
SDLS	472	11 393	472	472	2.16 ± 1.48
SDWW	1223	11 393	707	1223	1.11 ± 0.56
TLBW	1266	11 393	720	1266	14.93 ± 4.32
TLWW	1232	11 393	712	1232	96.92 ± 27.52

LS = litter size (newborns); SW = survivability at weaning (%); BW = birth weight (g); WW = weaning weight (g); SDLS = standard deviation of litter size (newborns); SDWW = standard deviation of weaning weight (g); TLBW = total litter birth weight (g); TLWW = total litter weaning weight (g).

m the maternal genetic effect of its dam, **c** the vector for the maternal permanent environmental effect; $\mathbf{z}_i$, $\mathbf{w}_i$ and $\mathbf{v}_i$ are the incidence vectors for **a**, **m** and **c,** respectively. The genetic effects **a** and **m** are Gaussian with

$$\begin{bmatrix} \mathbf{a} \\ \mathbf{m} \end{bmatrix} \sim N\left(\begin{bmatrix} \mathbf{0} \\ \mathbf{0} \end{bmatrix}, \begin{bmatrix} \mathbf{A}\sigma_a^2 & \mathbf{A}\sigma_{am} \\ \mathbf{A}\sigma_{am} & \mathbf{A}\sigma_m^2 \end{bmatrix} \right)$$

where **A** is the additive genetic relationship matrix and σ_a^2 and σ_m^2 are, respectively, the direct and maternal additive genetic variances and σ_{am} the genetic covariance between both genetic effects.

The third model was the heteroscedastic model (Model HE) developed by SanCristobal-Gaudy *et al.* (1998) which assumes that the environmental variance is heterogeneous and partially under genetic control, and was used to analyse LS and WW traits:

$$y_i = \mathbf{x}_i\mathbf{b} + \mathbf{w}_i\mathbf{m} + \mathbf{v}_i\mathbf{c} + e^{1/2(\mathbf{x}_i\mathbf{b}* + \mathbf{w}_i\mathbf{m}* + \mathbf{v}_i\mathbf{c}*)}\epsilon_i$$

where y_i is either LS of the female i and WW of the mother i of the pup, * indicates the parameters associated with environmental variance; **b** and **b*** are the vectors of the systematic effects; **m** and **m*** the vectors of the direct genetic effect of the mother, and **c** and **c*** the vectors of the litter effect; $\mathbf{x}_i$, $\mathbf{w}_i$ and $\mathbf{v}_i$ are the incidence vectors for systematic, animal and litter effects, respectively. Finally, $\epsilon_i \sim N(0,1)$. The genetic effects **m** and **m*** are distributed together and are assumed to be Gaussian:

$$\begin{bmatrix} \mathbf{m} \\ \mathbf{m}* \end{bmatrix} \sim N\left(\begin{bmatrix} \mathbf{0} \\ \mathbf{0} \end{bmatrix}, \begin{bmatrix} \sigma_m^2 & \rho\sigma_m\sigma_{m*} \\ \rho\sigma_m\sigma_{m*} & \sigma_{m*}^2 \end{bmatrix} \otimes \mathbf{A} \right)$$

where **A** is the additive genetic relationship matrix; σ_m^2 the maternal additive genetic variance of the trait; σ_{m*}^2 the maternal additive genetic variance affecting environmental variance of the trait; ρ the coefficient of genetic correlation; and $\otimes$ denotes the Kronecker product. The vectors **c** and **c*** are also assumed to be independent, with $\mathbf{c} \sim N(0, \mathbf{I_c}\sigma_c^2)$ and $\mathbf{c}^* \sim N(0, \mathbf{I_c}\sigma_{c^*}^2)$ where $\mathbf{I_c}$ is the identity matrix of equal order to the number of litters and σ_c^2 and σ_{c*}^2 are the litter effect variances affecting, respectively, the mean of the trait and its environmental variability (Ibáñez-Escriche *et al.*, 2008). The systematic effects (**b** and/or **b***) of the applied models included generation (eight levels), LS (from 2 to 17, 16 levels) except for LS and SDLS, sex (male and female for WW and also unknown for BW) and parity number (two levels). There were 1232 levels of permanent environmental effects (**c**) with 1232 levels of litters, and 12 637 levels of additive genetic effects or 11 393 when traits were assigned to the mother. Model HE was used in the experiment with data from Formoso-Rafferty *et al.* (2015) to predict the breeding values for BW environmental variability.

Genetic parameters under both models HO_m and Ho_i were estimated by using TM software (Legarra, 2008). The Model HE was fitted by using the GSEVM programme (Ibáñez-Escriche *et al.*, 2010). The results for each model were computed by averaging the results obtained from chains of Monte Carlo (Markov chain Monte Carlo (MCMC)) samples after running 1 000 000 iterations sampling one of each 100 iterations, and discarding the first 100 000. Genetic trends for the three models were analysed by averaging the predicted breeding values within line and generation and plotting them against generation.

For statistical inferences, LS, SW, WW, SDLS, SDWW, TLBW and TLWW were also analysed under a simple least squared model:

$$y_i = \mathbf{x}_i\mathbf{b} + e_i$$

in which y_i was either one of LS, SW, WW, SDLS, SDWW, TLBW or TLWW, and systematic effects in **b** were line × generation (17 levels) instead of generation, and the other systematic effects as described above, except TLBW and TLWW in which LS was excluded given that there were differences in mean LS between lines. Marginal posterior distributions of the difference between solutions for different lines, but 'same generation' were drawn to infer probabilities of response.

Results

Genetic parameters

Table 2 shows the estimated genetic parameters for the involved traits under a variety of models according to the analysed trait. Maternal heritabilities from Model HO_m ranged from 0.06 for SW to 0.34 for SDLS. Variance components at the trait level were consistent between Model HO_m and HE for LS and WW, the traits fitted under both models. The genetic variance concerning the environmental variability of WW and LS fell within the range reviewed by Hill and Mulder (2010). Genetic correlation between the trait and the environmental variability levels was −0.33 for WW and −0.81 for LS. Direct and maternal heritabilities as well as c^2 were computed as the ratio between the respective variance component and the phenotypic variance estimated under Model HO_i. Direct and maternal heritabilities were, respectively, 0.07 and 0.16 for WW, and 0.15 and 0.07 for BW, with a direct-maternal genetic correlation of 0.19 for BW and almost null for WW (−0.02).

Trends

Figure 1 shows phenotypic trends for the traits LS, SDLS, WW, SDWW, TLBW and TLWW across eight generations of selection. All of them performed irregularly across generations. However, a clear divergence between lines for LS and WW was exhibited, whereas for SDLS this was erratic with no clear differences between lines. Regarding the other traits, the low line had a higher performance than the high line for TLBW and TLWW, but lower for WW and SDWW. Looking at the marginal posterior distribution of the difference in the performance between the two lines in the last generation, the probability of these differences being higher (for WW and SDWW) or lower (LS, SW, SDLS, TLBW and TLWW) than zero were 100% for LS, 62% for SW, 100% for WW, 90% for SDLS, 100% for SDWW, 96% for TLBW and 25% for TLWW (Table 3).

LS, WW, SDLS and SDWW were analysed each under Model HO. LS and WW were also analysed with its respective environmental variability under Model HE. The evolution of

Table 2 *Mean (and standard deviation) of the marginal posterior distribution for the additive genetic variance (σ^2_a), maternal genetic variance affecting the mean and its variation (σ^2_m and σ^2_{m*}), the litter (or permanent for BW and WW) variances affecting the mean and its variation (σ^2_c and σ^2_{c*}), their genetic correlation (ρ_{mm*}), the direct-maternal genetic covariance (σ_{am}) and correlation (ρ_{am}), the direct and maternal heritabilities (h^2 and m^2) and the ratio between the litter (or permanent) and phenotypic variance (c^2), under models heteroscedastic (Model HE), individual homoscedastic (Model HO_i) or maternal homoscedastic (Model HO_m)*

Model HO_m		σ^2_m	σ^2_c	σ^2_e	m^2	c^2			
LS		1.70 (0.47)	0.79 (0.40)	5.95 (0.34)	0.20 (0.05)	0.10 (0.05)			
WW		0.86 (0.14)	1.38 (0.09)	1.52 (0.02)	0.23 (0.03)	0.37 (0.03)			
SDLS		0.83 (0.40)	–	1.57 (0.30)	0.34 (0.14)	–			
SDWW		0.03 (0.01)	0.02 (0.01)	0.26 (0.01)	0.09 (0.03)	0.06 (0.04)			
SW		15.12 (7.68)	22.99 (11.54)	193.53 (11.28)	0.06 (0.03)	0.09 (0.05)			
TLWW		68.03 (20.99)	44.11 (20.27)	286.58 (17.38)	0.17 (0.05)	0.11 (0.05)			
TLBW		0.54 (0.13)	0.16 (0.10)	2.31 (0.13)	0.18 (0.04)	0.05 (0.03)			
Model HE		σ^2_m	σ^2_c	σ^2_{m*}	σ^2_{c*}	ρ_{mm*}			
LS		1.83 (0.46)	0.72 (0.30)	0.23 (0.10)	0.11 (0.09)	−0.81 (0.13)			
WW		0.92 (0.13)	1.17 (0.09)	0.08 (0.03)	0.37 (0.03)	−0.33 (0.13)			
Model HO_i	σ^2_a	σ^2_m	σ^2_c	σ_{am}	σ^2_e	h^2	m^2	ρ_{am}	c^2
WW	1.09 (1.23)	1.02 (1.27)	1.04 (1.27)	1.08 (1.22)	1.38 (0.06)	0.07 (0.03)	0.16 (0.04)	−0.02 (0.24)	0.41 (0.03)
BW	0.03 (0.05)	0.04 (0.05)	0.11 (0.14)	0.08 (0.10)	0.02 (0.00)	0.15 (0.04)	0.07 (0.02)	0.19 (0.27)	0.28 (0.02)

BW = Individual birth weight; WW = weaning weight; LS = litter size; SDLS = litter size standard deviation; SDWW = weaning weight standard deviation; SW = survivability at weaning; TLWW = total litter weaning weight; TLBW = total litter birth weight.

LS and WW at the trait level can be assessed by the genetic trend from either HO and HE models, and their evolution at the environmental variability level can be addressed by either the genetic trend of SDLS and SDWW under the Model HO, and the genetic trend at the variability level of SD and WW under the Model HE. Figure 2 shows these comparisons by drawing together the genetic trends at the trait level of both models HO and HE across eight generations of selection. In the same Figure 2, genetic trends for SDLS and SDWW under Model HO are shown together with the corresponding trends at the environmental variability level of LS and WW when analysed under Model HE. The trends were almost identical across models for LS and WW at the trait level. There was a clear divergence between lines with the low line having a better performance for LS but worse for WW. However, the models performed very differently at the environmental variability level depending on the trait. Although this trend for WW under Model HE was virtually identical to that of the SDWW under Model HO, the same comparison for LS showed big differences between models leading to complete different conclusions. Figure 2 also shows how WW at both trait and environmental variability levels evolved in the same direction in agreement with that observed for BW (Formoso-Rafferty *et al.*, 2015). This was despite the genetic correlation between the WW mean and its environmental variability was negative, −0.33 (Table 2), unlike BW.

Phenotypic and genetic trends for SW are shown in Figure 3. The low line showed superiority in both trends. The phenotypic difference between lines was in fact obtained in the second generation and held across generations, with a throughout slope of 0.29 points of percentage per line and generation. From the genetic trends perspective, this slope was 0.16 points of percentage in the same period. The phenotypic trend exhibited a very important environmental influence of the generation effect but keeping the superiority of the low line along the whole experiment.

Information about the marginal posterior distribution of the difference between lines at the last generation, considering LS, SW, WW, SDLS, SDWW, TLBW and TLWW traits, is shown in Table 3. The results tended to lead to the same conclusion previously obtained from the genetic trends. Thus, to a greater or lesser extent, the low line performed better than the high line for LS, SW and SDWW (lower values) but worse for WW, by not showing any superiority of the lines for SDLS. As a combination of the performance of these traits, the low line also performed higher for TLBW. Phenotypic trends showed that TLBW and TLWW were higher in the low line for both traits across generations except TLWW in the last generation in which the low line was 3% lower.

As the selection was based on BW environmental variability as a maternal trait, we checked whether genetic trends for BW and WW had a similar pattern when these traits were assigned to the individual. Figure 4 shows the individual and maternal genetic trends when data were analysed under a model involving both effects. Divergence was observed in the same direction for both genetic effects showing a superiority of the high line. Even though a practically null genetic correlation between direct and maternal genetic effects, both showed genetic response as a consequence of their genetic correlation with the selection objective, the BW environmental variability.

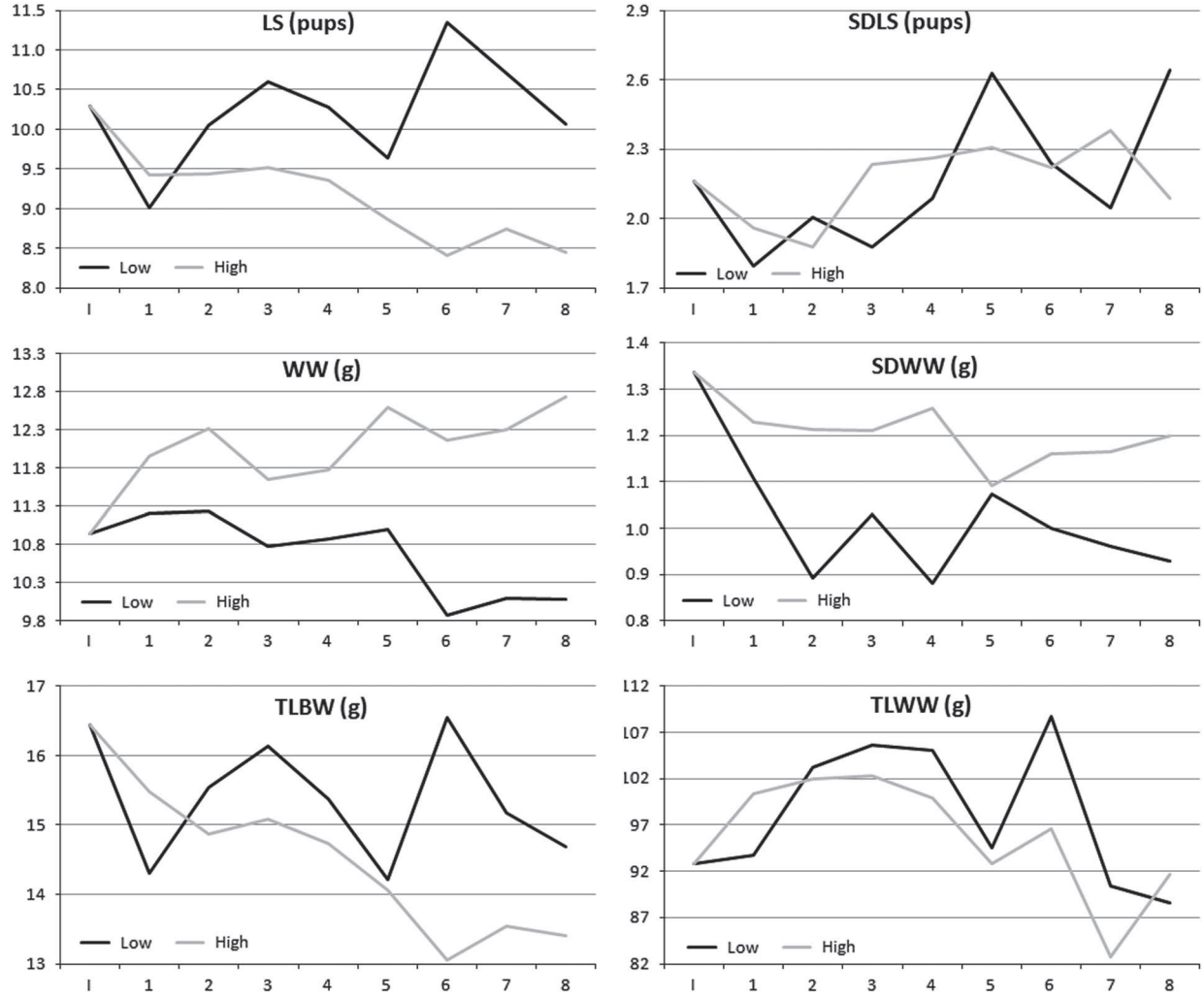

Figure 1 Phenotypic trends of litter size (LS), standard deviation of litter size (SDLS), weaning weight (WW), standard deviation of weaning weight (SDWW), total litter birth weight (TLBW) and total litter weaning weight (TLWW) across eight generations of selection.

Table 3 *Mean (*D*), standard deviation, and probability of* D > *0 or* D < *0 (*P*%) of the marginal posterior distribution of the difference between high and low environmental variability lines at the last generation for litter size (LS), survivability at weaning (SW), weaning weight (WW), litter size standard deviation (SDLS), weaning weight standard deviation (SDWW), total litter weaning weight (TLWW) and total litter birth weight (TLBW)*

	LS	SW	WW	SDLS	SDWW	TLBW	TLWW
D (high to low)	−1.67	−0.80	2.10	−0.56	0.27	−1.29	3.16
SD (*D*)	0.48	2.72	0.11	0.44	0.09	0.73	4.64
P% (*D* < 0)	100	62	0	90	0	96	25
P% (*D* > 0)	0	38	100	10	100	4	75

Discussion

Formoso-Rafferty *et al.* (2015) showed that selection for BW environmental variability was a successful process, but they did not show its implications on other production traits. Therefore, before applying this experience to livestock, the impact on some other welfare and productive traits should have to be addressed. In this paper, the correlated genetic trends affecting such other interesting traits were studied.

First, genetic parameters were estimated. In this case, most of the estimates were obtained by using maternal models because previously published results (Pun *et al.*, 2013) showed the convenience of analysing BW environmental variability as a maternal trait. The maternal heritability obtained for the traits were within the range of previous results published on mice (Ibáñez-Escriche *et al.*, 2008). The estimate of maternal heritability for SW was slightly lower than the value of 0.10 reported in pigs (Mesa *et al.*, 2006).

BW and WW were also analysed under direct-maternal animal models due to its important individual genetic base and to see how selecting mothers would impact on the evolution of the direct genetic effect. When comparing estimated parameters for WW across models, it should be remembered that in the maternal model, the maternal effect is also gathering half the individual direct effect, and maternal variance also gather a quarter of the individual

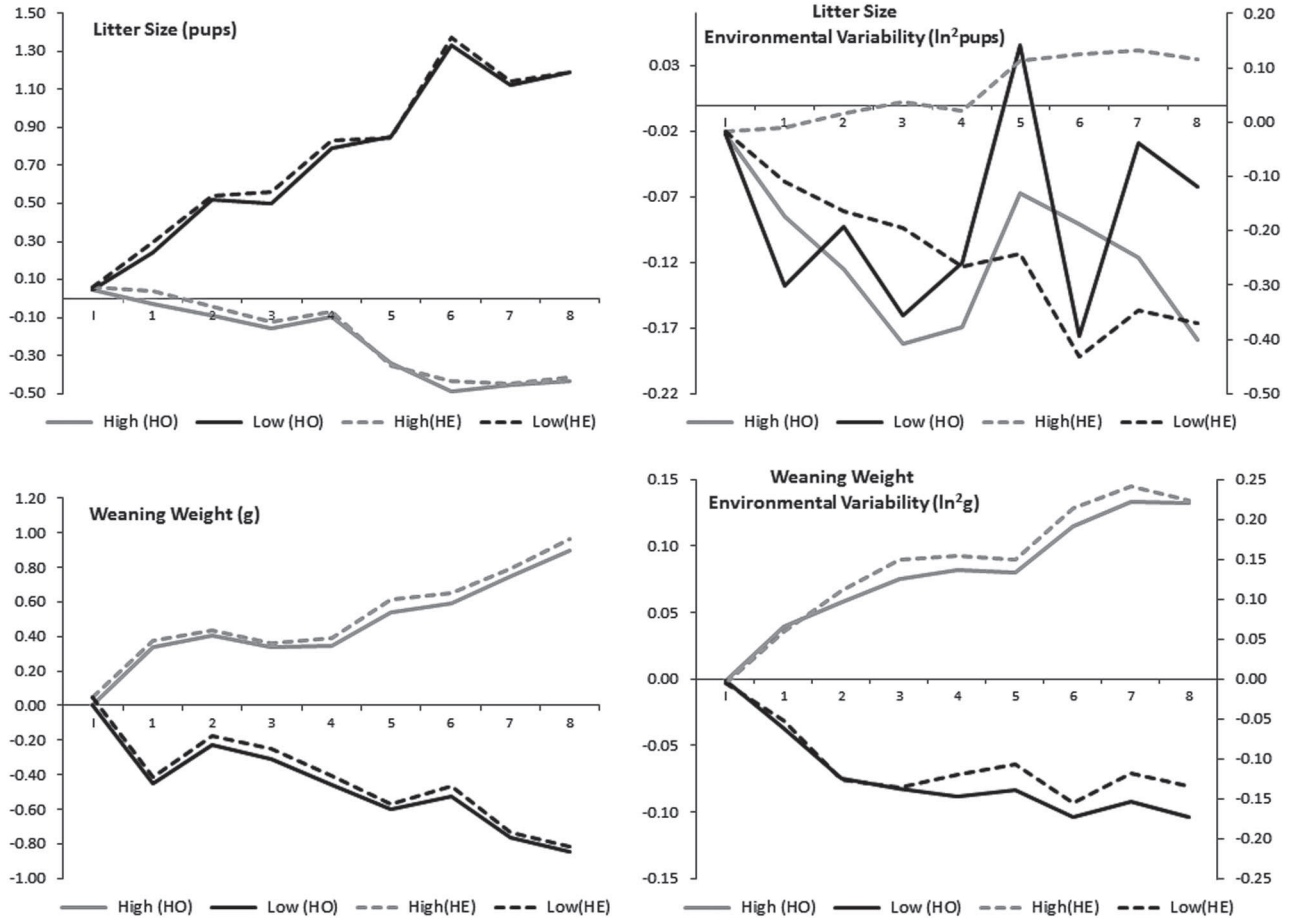

Figure 2 Genetic trends of the mean (left) of litter size (top) and weaning weight (bottom) and their respective environmental variability (right) by fitting Homoscedastic (HO) and Heteroscedastic (HE) models across eight generations of selection.

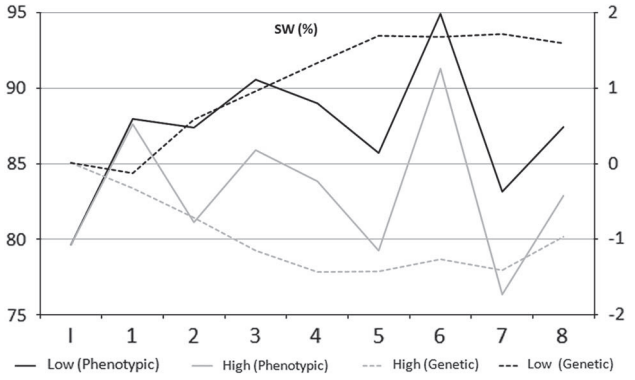

Figure 3 Genetic (right axis) and phenotypic (left axis) trends of the percentage of survivability at weaning (SW) across eight generations of selection.

additive genetic variance. Results were not completely equivalent given that a direct-maternal genetic covariance was also fitted. This led to a greater reduction of the maternal variance component but increasing the litter variance component.

Genetic correlation estimates between direct and maternal effects for WW and BW were low. These results are in contrast with usual high negative genetic correlations found in the literature (Cervantes *et al*., 2010). Specifically, this genetic correlation found for WW suggests that genetic trends in this population would be expected to be independent in both genetic effects. However, looking at Figure 4, both genetic trends evolve in the same direction, with this evolution being roughly proportional to the variance of the effect. This would suggest that the selection criterion, the BW environmental variability, was correlated with both direct and maternal WW genetic effects. The mean WW was 2.10 g heavier in the high line than in low line, at the end of the selection process (Table 3). Looking at Figure 4, this superiority would be caused mainly by the maternal effect (Eisen, 1978). These trends were in agreement with other authors (Eisen, 1978; Bayon *et al*., 1987).

A detail worth mentioning refers to the performance of Model HE that virtually had identical genetic trends than the Model HO at the trait levels for both LS and WW. However, Figure 2 shows the different performance of models HO and HE for LS and WW on the variability level. On this level, the performance of the Model HE was fairly similar to that of Model HO for WW but very different for LS. There are several differences between SDWW and SDLS that explain the different performances of the model. The number of records

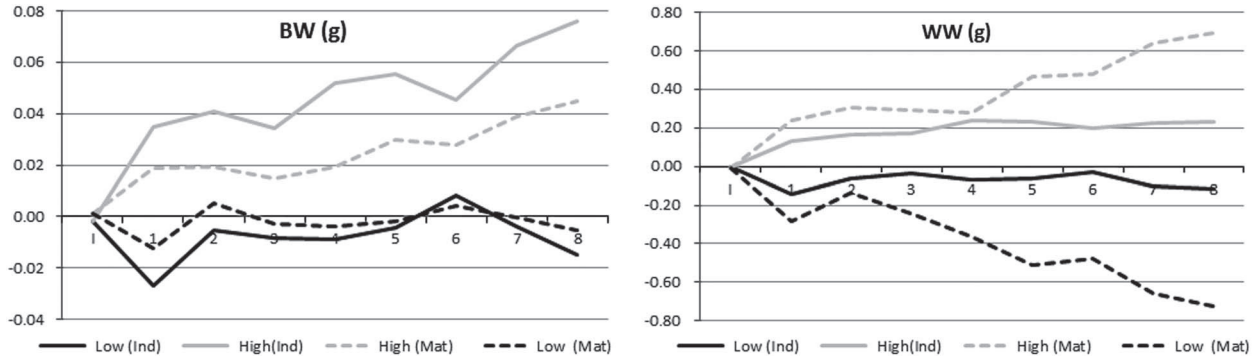

Figure 4 Direct (Ind) and maternal (Mat) genetic trends for birth weight (BW) and weaning weight (WW) across eight generations of selection.

for SDLS and SDWW were, respectively, 472 and 1223, and that standard deviation was computed with only two records in the first case, and with an average of 8.60 records in the second case. Standard deviations were poorly computed within individuals with two records at maximum. Then the phenotypic values, the genetic values and the corresponding trends were badly estimated. As a consequence, genetic correlation between the trait and environmental variability levels of LS was also poorly estimated. In this case this correlation resulted in a extreme negative value (−0.81), conditioning a highly related but inverse genetic trends between both levels. Thus, the genetic trend at the environmental variability level (Figure 2) became dramatically different from that of SDLS under Model HO (Figure 2), and also different from the phenotypic trend (Figure 1). A second conclusion can be drawn from this study. It has been shown that predicted breeding values for the environmental variability are unreliable with insufficient information under Model HE. However, in the scenario in which data provide enough information, both approaches perform mostly equal. Theoretically, there are more benefits in Model HE. It can simultaneously fit systematic effects on the trait and variability levels in one step, and it takes into account the whole structure of the data by using one residual per observation instead of one record per individual. Therefore, it would be theoretically preferred, but both models perform similarly in practice under robust information. The results show that the selection response evaluated with either models HO or HE are in good agreement. This can be considered as an argument in favour of the results found under Model HE, and therefore also in favour of the genetic parameters used in the analysis of the process of selection (García *et al.*, 2009).

The positive relationship between the phenotypic and genetic trends of WW with its environmental variability (Figure 2) contradicted the obtained negative genetic correlation between them (−0.33, Table 2). Computed genetic correlation between predicted breeding values of the trait and the variability for WW, not shown, resulted negative within line and generation, but both genetic correlations between them and the selection criterion, the breeding value for the variability level of BW, were positive. It was a welcome surprise to realise how the negative genetic correlation could be bypassed to obtain both indirect genetic trends in the same direction by using as criterion a third positive genetically correlated trait. An interesting implication of this would be that selecting for reducing WW variability would lead to favourable response in both levels, increasing the WW mean and reducing its variability. There was therefore, a relationship between the variability at birth and at weaning. It could be partially explained because, in the low line, pups tend to weigh all the same at birth, having less competition for sucking, and tending to have consequently the same growth.

The experiment was carried out as a model for livestock species. Therefore, consequences on productivity and welfare are a concern. Regarding the consequences of selecting for BW environmental variability, the low line was clearly better for LS and SW. For the case of SW, and from a phenotypic point of view it seems that a strong response occurred at generation 2 and the difference between lines was maintained later on, but did not change under selection. Even this superiority was clear, the evolution was not always growing across generations and its magnitude varied depending on the method used to address it. There were identical genetic and phenotypic trends of 0.1 pups per line and generation with a final total rough difference of 1.65 pups between lines.

All these traits have been shown in the past to be related. Selection for LS should be accompanied by selection for mortality and/or BW traits. Losses from birth to weaning and the minimal BW in the litter were proposed as potential traits for selection against piglet mortality (Damgaard *et al.*, 2003; Wolf *et al.*, 2008). The effect of LS on mortality and growth can be reduced markedly in homogeneous litters, which results in more efficient growth in rabbits of low BW. In addition, heterogeneous litters would be more prone to diseases that infect other pups in the same litter (Poigner *et al.*, 2000). However, grading BW and fostering methods would improve preweaning survival (Perrier, 2003). The results reported by García and Baselga (2002) indicate that selection for LS at weaning offers a tool to improve reproductive traits for weaning in rabbits, improving significantly ovulation rate, without significant negative changes in prenatal survival.

Thus, low line performed better for LS and SW with the consequent benefits in productivity and welfare. García *et al.* (2012) tested the hypothesis that in the rabbit a selection for LS residual variance affected animal welfare. This was

partially confirmed in the present study. However, the mice in the low line were smaller both at birth and at weaning, which would be accompanied by a lower economic benefit and for some the state of their welfare might be worse. Thus, for example, thinking of the sale of animals at weaning, after eight generations of selection, a weaned animal from the high line weighed 26% more than one from the low line (12.72 *v.* 10.09 g). Although the animals were selected based on the performance of their mothers, both genetic trends, direct and maternal, were growing through generations. This difference could have been due in part to increased LS of the low line.

Summarising, considering LS and survival, low line was preferable from the welfare perspective, but its superiority from the productivity point of view was not clear. On the one hand the low line performed a higher LS and SW but with animals weaned with lower weight. However, the low line did not perform less total weight as shown by the final TLWW after eight generations.

It seems that robustness was higher in the low line as understood by Mormede and Terenina (2012) as less sensitivity with respect to environmental effects as indicated by a low variation having benefits in the animal welfare, but this still remains unclear. Other researches, for example, on growth after weaning, lifetime, number of weaned offspring during an uncensured life and responses to environmental changes should be carried out in order to understand robustness better.

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