# Modulating birth weight heritability in mice[1]

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**ABSTRACT:** Expected genetic response is proportional to the heritability of the trait, and this parameter is considered inherent of a specific trait in a particular population. However, models assuming heterogeneity in residual variance lead to different estimates of heritability across combinations of systematic (environmental) effects. Modifying the residual variance of the birth weight by artificial selection was shown to be feasible in a divergent selection experiment in mice. The objectives of this work were to 1) estimate the evolution of the heritability of birth weight in mice in the mentioned experiment, and 2) estimate different heritability regarding systematic effects. Data came from eleven generations of a divergent selection experiment to modify the residual variability of birth weight in mice. A total of 15,431 birth weight records from 959 females and 1,641 litters in combination with 14,786 pedigree records were used. The model used for analysis included generation, litter size, sex, and parity number as systematic effects. Each record of birth weight was assigned to the mother of the pup in the model which assumes that the residual variance is heterogeneous and partially under genetic control. Differences in heritability between lines reached values of 0.06 in the last generations. Choosing the most extreme values of systematic effects, the birth weight heritability ranged from 0.04 to 0.22. From these results, the possibility of modulating the heritability for this trait could be explored in 1 of 2 ways: selecting to decrease the residual variability, or choosing the specific levels of the systematic effects.

**Key words:** birth weight, heritability, mice, residual variability, selection experiment

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## INTRODUCTION

Genetic response is theoretically proportional to the heritability of the trait (Falconer and Mackay, 1996) and it is accepted that manipulating this parameter is unfeasible because it is considered as an inherent parameter for a particular trait in a particular population. However, under a model assuming heterogeneity in the residual variance, different estimated heritabilities can be obtained for each combination of levels of the systematic effects (Gutiérrez et al., 2006; Ibáñez-Escriche et al., 2008a). This is important, because by not accounting for heterogenous residual variance can have a high impact on the breeding prediction values and, therefore, in the response to selection (Hill, 1984; Robert-Granié et al., 1999; Sorensen and Waagepetersen, 2003). Furthermore, to our knowledge, a study of heritability heterogeneity regarding systematic effects has never been addressed. Consequently it might be important and relevant in optimizing genetic selection of breeding programs. Interest in the genetic control of the residual variability is also growing for many other reasons (Högberg and Rydhmer, 2000; Damgaard et al., 2003; Bolet et al., 2007; Garreau et al., 2008). The homogeneity of animal production would decrease the cost of handling and production that ultimately would increase the profitability of the farm and increase animal welfare.

Formoso-Rafferty et al. (2016a) showed that modifying the residual variance of birth weight (**BW**) by artificial selection was feasible in a divergent selection experiment in mice. Therefore, the cumulated information from such an experiment could be use-

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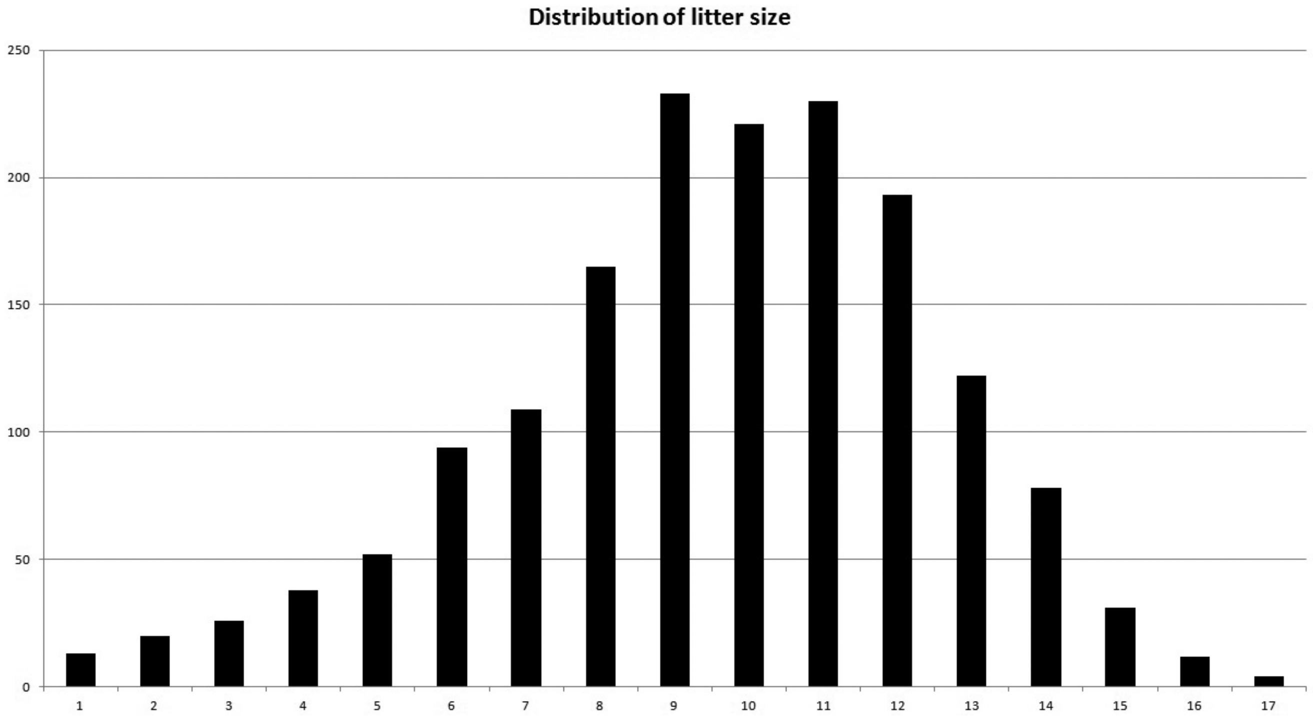

**Figure 1.** Distribution of litter sizes across the experiment.

ful to address how heritability can be modified across generations of selection for residual variance of BW. As a consequence, this work has 2 main objectives: first, to study whether the heritability of birth weight can be modified through the selection for the residual variance of BW, and second, to study the impact of systematic effects on the heritability of BW.

## MATERIALS AND METHODS

All data used in this study came from the successful divergent selection experiment conducted to modify the residual variability of birth weight by Formoso-Rafferty et al. (2016a). It was started from a created mouse population originating from a balanced genetic contribution of 3 inbred mice lines: BALB/c, C57BL and CBA. The origin of the experimental population was used for other selection experiments (Fernández and Toro, 1999; Gutiérrez et al., 2006; Ibáñez-Escriche et al., 2008a; Moreno et al., 2012; Pun et al., 2013; Formoso-Rafferty et al., 2016a).

Initially, the three-way cross population was maintained in panmixia for more than 40 generations to ensure a high level of both genetic and phenotypic variability. Randomly selected from this population were 64 males and 64 females. These pairs were also randomly mated, 1 male with 1 female having 2 litters each, to evaluate the mothers for the residual birth weight variability of their offspring and the additional purpose of setting up both variability lines.

A total of 43 males and 43 females per line of offspring from the 10 mothers with the highest and lowest predicted genetic value for birth weight residual variability, were selected to establish the first generation of the high and low variability lines. This process was followed within line over 11 additional generations. This procedure was improved by implementing weighted selection, allowing more descendants from the best mothers if mean co-ancestry was not increased. A simulated annealing (Formoso-Rafferty et al., 2016a) 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 final evaluation dataset contained a total of 15,431 records of BW from 1,641 litters of 959 females. The mean (± the standard deviation) for the litter size (newborns) and for the BW (g) were 9.60 (± 2.91) and 1.56 (± 0.21), respectively. Figure 1 shows the distribution of the litter sizes across the experiment. The total number of individuals included in the analyzed pedigree was 14,786 that included 5 generations back of previous known pedigree in the panmitic population.

For the present study, a heteroscedastic (**HE**) model developed by SanCristobal-Gaudy et al. (1998) was used. It is assumed in the model that the residual variance is heterogeneous and partially under genetic control:

$$y_i = \mathbf{x}_i\mathbf{b} + \mathbf{w}_i\mathbf{m} + \mathbf{v}_i\mathbf{c} + e^{\frac{1}{2}\left(\mathbf{x}_i\mathbf{b}^* + \mathbf{w}_i\mathbf{m}^* + \mathbf{v}_i\mathbf{c}^*\right)}\varepsilon_i$$

where $y_i$ is the BW of the *i* individual,* indicates the parameters associated with residual variance; **b** and **b*** are the vectors of the systematic effects; **m** and **m*** are the vectors of the maternal genetic effect of the mother, and **c** and **c*** are the vectors of the litter effect; **x**i,**w**i and **v**i are the incidence vectors for systematic, animal, and litter effects, respectively. Finally, $\varepsilon_i \sim N(0,1)$. The genetic effects **m** and **m*** are distributed together and are assumed to be Gaussian:

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

where **A** is the additive genetic relationship matrix; $\sigma_m^2$ is the maternal additive genetic variance of the trait; $\sigma_m^2$ is the maternal additive genetic variance affecting residual variance of the trait; ρ is the genetic correlation between the trait and its residual variability, and ⊗ denotes the Kronecker product. The vectors **c** and **c*** are also assumed to be independent, with $\mathbf{c} \sim \mathrm{N}\left(\mathbf{0}, \mathrm{I}_\mathbf{c}\sigma_\mathbf{c}^\mathbf{2}\right)$ and $\mathbf{c}^* \sim \mathrm{N}(\mathbf{0}, \mathrm{I}_\mathbf{c}\sigma_{\mathbf{c}^*}^2)$ where $\mathrm{I}_\mathbf{c}$ is the identity matrix of equal order to the number of litters and $\sigma_\mathrm{c}^2$ and $\sigma_{\mathrm{c}^*}^2$ are the litter effect variances affecting, respectively, the mean of the trait and its residual variability (Ibáñez-Escriche et al., 2008a).

First, the model applied included generation (12 levels of data, 11 of selection), litter size (from 2 to 17, 16 levels), sex (3 levels: male, female, and unknown) and parity number (2 levels) as systematic effects in **b** and **b***, and the litter (1,641 levels) and additive genetic effect (14,786 levels) as random effects besides the residual effect.

Second, modify the model to assess the genetic trend in the experiment to estimate a particular residual variance for each line and generation. Thus, **w**i m* was removed from the equation and the generation systematic effect was replaced for a new line* generation systematic effect, with 23 levels, 1 for the founder generation and 11 for each generation within line. This effect should capture the non-fitted genetic effect for residual variability. Genetic trends were then assessed from the solutions of this particular effect.

There were several estimations of heritability for the traits under this procedure because residual variance varies among levels of the **b** effects (Ibáñez-Escriche et al., 2008b). In this case, the phenotypic variance ($\sigma_p^2$) is not unique and it must be recalled as $\sigma_{p_i}^2$ because it is conditioned to the levels of the systematic effects thus affecting the residual variability (**b***). Also the heritability parameter ($h^2$), the usual ratio of additive to phenotypic variance must be called $h_i^2$. Under the He model, these parameters are:

$$\sigma_{p_i}^2 = \sigma_m^2 + \sigma_c^2 + \sigma_{e_i}^2 = \sigma_m^2 + \sigma_c^2 + e^{\left(Xb_i^* + \frac{1}{2}\sigma_{m^*}^2 + \frac{1}{2}\sigma_{c^*}^2\right)}$$

and

$$h_i^2 = \frac{\sigma_m^2}{\sigma_m^2 + \sigma_c^2 + \sigma_{e_i}^2} = \frac{\sigma_m^2}{\sigma_m^2 + \sigma_c^2 + e^{\left(\mathbf{Xb}_i^* + \frac{1}{2}\sigma_{m^*}^2 + \frac{1}{2}\sigma_{c^*}^2\right)}}$$

### *Heritability within Levels of Systematic Effects*

From the expressions above, specific residual variances can also be estimated for particular levels of systematic effects. To keep the estimability of the corresponding linear combination, solutions for all the levels of each of the other systematic effects were averaged within effect and added to the solution for that particular desired level of the systematic effect. Therefore the residual variance for a particular level *l* of a systematic effect *s* was:

$$\sigma_{e_{sl}}^2 = e^{\sum_{i=1,systematics}^{i \neq s} \left( \sum_{j=1,n_s} \frac{\hat{b}_{ij}}{n_s} \right) + \hat{b}_{sl} + \frac{1}{2}\sigma_{m^*}^2 + \frac{1}{2}\sigma_{c^*}^2}$$

and the corresponding heritability:

$$h_{sl}^2 = \frac{\sigma_m^2}{\sigma_m^2 + \sigma_c^2 + \sigma_{e_{sl}}^2}$$

The model was solved by using the GSEVM program (Ibáñez-Escriche et al., 2010) and was used across the experiment to predict the breeding values for birth weight residual variability. The results for the model were computed by averaging the results obtained from chains of Monte Carlo (**MCMC**) samples after running 1000,000 iterations sampling one of each 100 iterations, and discarding the first 100,000. Since Bayesian procedures were used, inferences were based on probabilities obtained from the marginal posterior distributions of the parameters or their combinations. The mean of such marginal posterior distributions will be considered as the estimates across the text.

## RESULTS

The means and standard deviations (in brackets) of the marginal posterior distributions for the BW genetic parameters were estimated with all the records belonging to the 12 generations under the heteroscedastic model. Regarding $\sigma_m^2$ it was $5.22 \times 10^{-3}$ ($0.79 \times 10^{-3}$). The estimates for $\sigma_c^2$ was $10.40 \times 10^{-3}$ ($0.64 \times 10^{-3}$).

The parameters affecting residual variability of the trait were also estimated by the model ignoring additive genetic variance. The estimate for $\sigma_{\mathrm{c}^*}^2$ was 0.327 (0.021). The model provided different estimate heritabilities regarding systematic effects. The estimate obtained by averaging all levels of systematic effects was 0.133 (0.019), which can be understood as the estimate of the parameter under an intermediate effect of the different litter sizes, sex levels, and parturitions.

### *Evolution of Heritability across Lines and Generations*

Estimates of BW heritability in each generation for both high and low variability lines are shown in Fig.

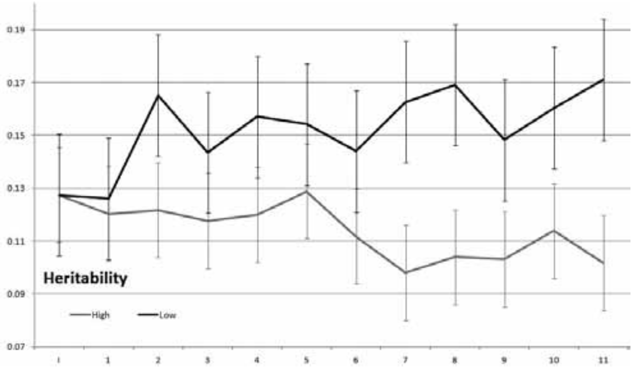

**Figure 2.** Means of the marginal posterior distributions of the heritabilities obtained from a heteroscedastic model across generations and within lines and their standard deviations.

2. Divergence was observed from the first generation of the experiment when the lines were setup, and remained across the subsequent generations. Evolution of the estimated differences between the heritabilities in the low and the high line and their standard deviations across 11 generations of selection is shown in Fig. 3. The difference was roughly 0.069 (0.014) in the 11th generation and increasing, which is equivalent to more than half a point of difference per generation on average. The intervals did not include the zero from the second generation of selection onward. As reported by Formoso-Rafferty et al. (2016a), the null response for residual variability of birth weight was well noted in the first generation of selection, that followed by an important success in the second generation and maintaining the heritability difference between lines from this generation to the 6th. In Fig. 2 it is also shown that this difference was stronger due to the response obtained in the low variability line (0.043 of difference compared to the founder generation) than in the high variability line (0.026). Heritability was between 5% and 68% greater in the high line than in the low line across generations.

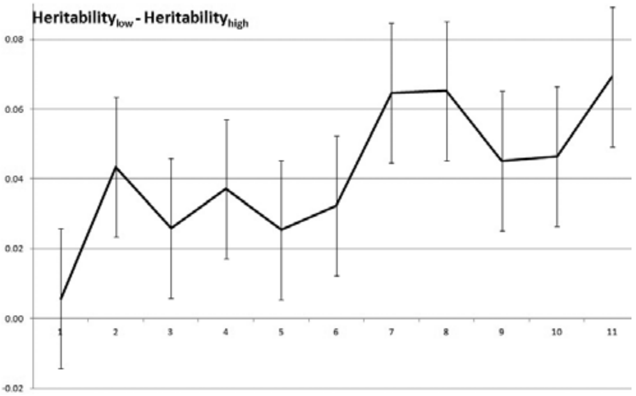

**Figure 3.** Evolution of the means of the marginal posterior distributions of the differences in heritability between the low and the high line and their standard deviations across 11 generations of selection.

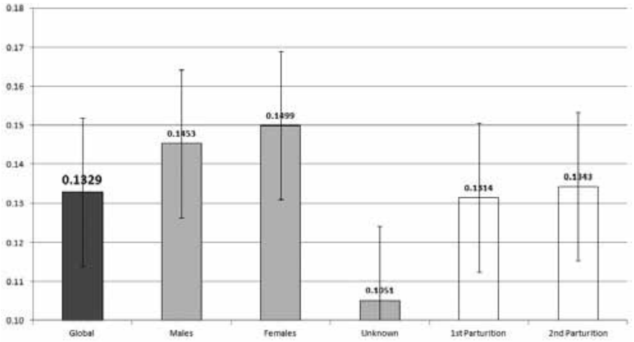

**Figure 4.** Means of the marginal posterior distributions of the global heritability and for those obtained for the levels of the systematic effects sex and parturition and their standard deviation.

### *Heritability within Levels of Other Systematic Effects*

Figure 4 shows the estimated BW heritability when all solutions for the systematic effects were averaged within effect and summed up, to be considered as the global heritability. Figure 4 also shows the estimated heritabilities corresponding to particular levels of sex effect (males, females, or unknown), or parturition effect (first or second).The probability of female heritability being higher than a male one, was 98% but this difference was not really relevant (0.005). However, that probability was 100% when comparing female or male heritabilities with unknown sex heritability, these differences were more noticeable: 0.044 for females and 0.040 for males. Comparing heritabilities regarding the number of parturitions, they were respectively 0.1313 and 0.1341 for first and second parturition with no significance of the difference: 82% of probability of the second parturition being higher than the first one.

The evolution of BW heritability estimates regarding litter size is shown in Fig. 5, including the standard deviations of their marginal posterior distributions. Heritability estimates increased with litter size. Special mention should also be made to the heritability estimate when only 1 or 2 pups were born, with an extremely low heritability showing the enormous residual variance being estimated in these group. Heritability estimates for litter sizes from 3 to 7 pups remained roughly stable, but increased from this litter size onward.

## DISCUSSION

Different BW heritability estimates, with this trait being attributed to the mother of the pup, were reported in the present study by using the information collected in a divergent selection experiment for BW residual variability. The experiment used to provide the data was especially designed on the basis of the conclusions reached from a previous experiment showing that the BW residual variability was essentially under maternal control (Pun et al., 2013). The experiment was success-

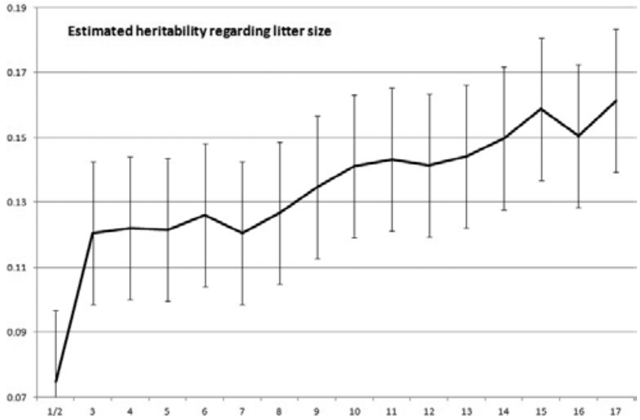

**Figure 5.** Means of the marginal posterior distributions for the heritabilities obtained for the levels of the litter size effect and their standard deviations.

ful (Formoso-Rafferty et al., 2016a) and showed a divergent response for the selection BW residual variance. Formoso-Rafferty et al. (2016b) showed that this selection also contributed to a positive correlated response on traits related to welfare. Nevertheless, an additional benefit of the low variability could be the increase in heritability that would help a higher artificial selection response. Argente et al. (2012) reported that selection to reduce residual variance of litter size could also increase heritability of litter size. This fact could be relied on to increase the response to selection of a trait that usually responds poorly to selection because of its low heritability. However, to our knowledge, changes in heritability across generations of selection for residual variance had not previously been studied.

The experiment, and also this paper has been performed in mice, but as a hypothetical animal model for livestock mammals. The shorter generation interval of this experimental population allowed arriving fast to conclusions, and these will probably be valid to implement in animal production practices. In this particular work the possibility of increasing the heritability seems feasible and useful in practical scenarios.

Global BW heritability estimated with the whole dataset resulted in 0.127. Pun et al. (2013) in a similar population with common origin estimated a heritability of 0.27. In this case the trait was assigned to the pup, which explains the differences between the estimates. In the present study the additive effect was attributed to the mother thus accounting for a quarter of the additive effect when assigned to the pup. In this context the results were in close agreement.

Probably the best model would fit both individual and maternal genetic effects for the trait and only the maternal genetic effect for the residual variability, but the software used to carry out the analysis did not allow such a complex model. Therefore, the rest of the discussion below will focus on a lower heritability magnitude as if the trait was attributed to the individual, probably underestimating the consequences of modulating the residual variance.

The possibility of modulating the heritability for this trait can be explored by selecting to increase or decrease the residual variability. Such modification of the heritability would imply changes in the genetic response to artificial selection. In this context, significant and relevant differences in heritabilities already appeared at the second generation of selection. The selection process was unsuccessful in the first generation as a consequence of a bad estimate of the genetic correlation between the trait and its residual variability at the generation setting up the divergent lines, but the experiment became successful afterward. The global trend in the heritability difference was positive but irregular as a consequence of the high statistical noise involved in the selected trait. Nevertheless, after generation 6 the differences of heritability between lines were clearly different from zero. The greatest difference was 0.069 reached at the 11th generation, which became 68% greater heritability in the low variance line. Note that this difference will imply that selection for BW in the low variability line will correspond to a higher selection response to artificial selection in the high variability line. From a practical point of view, although the final result of the selection process was positive, it is not clear how long the selection process has to be kept. However, deciding a first selection to improve the heritability is not clearly worthwhile as it implies a delay in the selection of the trait. By looking at Fig. 2 and 3 it does not help much in deciding how many generations of selecting against residual variance are required. From a phenotypic point of view, it seems that the selection to increase the heritability would have been clearly successful in the 2, 7, and 10 generations, but not in other generations. Regarding the usefulness in animal breeding, the time elapsed involved to get a higher heritability is of concern. The final result of the selection process was positive, but it is not clear how long the selection process has to be kept. Moreover, in this case the selection for the residual variability had a negatively correlated response for BW, producing smaller animals in the low variability line, an undesired effect in the meat trade (Formoso-Rafferty et al., 2016b). A compromise solution could be to include the predicted breeding value for the residual variability among the objectives to be combined in a selection index. Therefore, it is clear that the BW heritability was modified by residual variance selection, but it is not clear if it is the optimal strategy for increasing BW. A further study will be needed to answer this question, but this was not the aim of this paper.

The possibility of modulating the heritability for this trait could alternatively be explored in a different way: choosing the most appropriate combination of levels of the systematic effects. A detailed discussion about heterogeneous heritability regarding systematic effects can be found in Sorensen and Waagepetersen (2003), Ros et al. (2004) and Ibáñez-Escriche et al. (2008b). Selecting to modify the residual variability is thus not the only possibility to deal with the modulation of the heritability. Restricting the information to particular levels of systematic effects would anyhow decrease the residual variance, but under an heteroscedastic framework, it could be more strongly reduced if records belong to the levels with the lowest residual variance. Note that our understanding of how heritability varies between levels of systematic effects can be used to design restricted performance by recording the maximized heritability and thus save resources by focusing efforts. This would not imply excluding animals for selection, but only restricting the performances to be registered. This would apply when designing the performance recording to optimize resources. For example, registering female BW instead of male BW would result in a 3% higher response to selection. However, genetic progress not only depend on the heritability and other parameters would have to be accounted. For example, it is not clear that this restriction is worthwhile since by reducing the amount of data it would reduce accuracy to predict breeding values with the resulting consequence of reducing the genetic response. Also the impact of a wrong model could have impact on the true genetic response. Gutiérrez et al. (2006) reported that the use of heteroscedastic models would reduce the bias in the predicted breeding values, which obviously would reduce the genetic progress.

Another interesting point to take into account is analyzing the consequences of not considering the sex as a systematic effect in the model, whatever homoscedastic or heteroscedastic models is fitted. Heritability for males and females became almost 30% higher than when the sex is unknown. Although it could raise the possibility of not registering the sex to make it easier and accelerate the handling of animals and reduce costs, it has been shown in the present study that taking into account the sex in the model, will largely compensate in terms of heritability and consequently in the response to selection.

Heritability differences between first and second parturition were not relevant or significant in this case, showing that it should be better registering all of parturitions to achieve a higher amount of records and higher accurate predictions of breeding values.

Important differences in heritability were also found for litter size. Litter sizes that were small had much greater residual variance and consequently a much lower heritability. Nevertheless, litters of small size were very few: 13 with 1 pup and 20 with 2 pups over 1,641 litters and these small litters we included together in the same level of the systematic effect. From, 3 to 7 pups of litter size the heritability was similar which would indicate that there was not influence of space limitation in the uterus for these litter sizes. Relationships between uterine space, embryonic survival and litter size have already been clearly established in pigs and rabbits (Lamberson et al., 1991; Johnson et al., 1999; Ruíz-Flores and Johnson, 2001, Ziadi et al., 2013). Nevertheless, there was a roughly linear increase in the heritability from 8 to 15 litter size suggesting that there is not enough room for free growth to maximize the potential growth of the individuals, thus all pups tended to be smaller but had the same body size. The number of litters with a higher litter size was also uncommon, four of 17 pups and 12 of 16, which justifies the non-linearity of the trend at that level of litter sizes. These were not grouped in a single level since the total number of pups belonging to each of the litter size classes seems to be enough for a good estimation of the effect of the litter size. Thus, it appears that populations with greater litter size will have greater BW heritability. A wider and more useful thinking can be reached: when deciding what population would be useful to select for increasing BW, the one with the highest litter size would be expected to have higher selection response. However, this has to be done with caution and take into consideration the current BW of the population, since higher litter sizes are usually accompanied with lower individual BW (Formoso-Rafferty et al., 2016b).

The possibility and utility of modulating the heritability by selection and/or by properly restricting information, is clearly addressed when looking at the extremes. Thus, the maximum and the minimum heritabilities in this data set were respectively 0.217 and 0.037. The maximum heritability of 0.217 corresponds to the females born in a litter of 17 pups of second parturition in the 11th generation of selecting to decrease the residual variability. The minimum heritability of 0.037 was estimated for animals of unknown sex born in a litter of only 1 or 2 pups in the first parturition of the animals born after 8 generations of selection to increase the residual variability. Since selection response would be proportional to the heritability, the success of artificial selection would be six-fold greater in the first case. Note that the only manipulation involved would be not recording the performance of individuals classified in the less favorable levels of the effects regarding heritability.

The possibility of modulating heritability by selection and restricting the information has been shown in this paper. Animals belonging to the low variability line had already been shown advantageous because of their robustness and welfare (Formoso-Rafferty et al., 2016b). They have been shown to be also preferable from the point of view of the heritability, the consequence of a lower residual variance under an assumed equal genetic variance. Selecting to increase the heritability seems to be likewise possible, but it must be done with caution.

Including a new selection criterion would have implications to any other trait that the new one is genetically correlated with. Particularly, genetic correlation between a particular trait and its variance would have impact in the correlated responses depending on the value of the genetic correlation between the mean of a trait and its residual variability. For example, Formoso-Rafferty et al. (2016a) showed a dramatic response of the mean BW in the first generation of this experiment due to an overestimated genetic correlation. Likewise, selecting under homoscedastic models would modify the variability of the trait in the extent of the value of that genetic correlation. The inclusion of reducing the residual variability in a selection index could be an opportunity, but further research is needed. On the other hand, the observed results in this experimental population would have to be confirmed in livestock species, such as pigs or rabbits. Increasing the heritability could accelerate the genetic response in their breeding programs.

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