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Inbreeding depression for litter size in two mice lines under divergent selection for environmental birth weight variability using genomic data

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Abstract

Inbreeding depression (ID) is usually observed as reduced survival and fertility and may have a variable impact in different populations. The aim of this study was to estimate ID from genomic and pedigree data in the litter size (LS) of the high variability (H-Line) and the low variability (L-Line) mice lines divergently selected for environmental birth weight variability. Of these, the L-Line performed better on traits related to robustness. A total of 1587 females from 26 selection generations were genotyped with a high-density SNP array. LS data of 732 L-Line and 648 of H-Line animals were used. The following were calculated: pedigree inbreeding coefficient (F_{PED}), genomic inbreeding derived from different genomic matrices (F_{NEJ}, $F_{L\&H}$, F_{VR1}, F_{VR2} and F_{YAN}), from runs of homozygosity (F_{ROH}) and from homozygosity by descent probabilities (F_{HBD}). F_{ROH} were calculated in the 19 autosomes (CHR). F_{ROH} and F_{HBD} were divided into nine lengths and age classes, respectively. All the inbreeding coefficients were standardized by the mean inbreeding coefficient of the 1st generation. Regression coefficients (m) obtained from genomic data were between −3.71 with F_{VR2} and −5.09 with F_{HBD} in the H-Line, and that estimated from F_{PED} was −5.67. In the L-Line the m obtained from genomic data were between −3.52 with F_{VR2} and −4.55 with F_{HBD}, and that obtained with F_{PED} was −4.08. Significant ID effects were detected in CHR13 in the H-Line and CHR1 and CHR9 in the L-Line. The m negative trended to be lower as the ROH length increased. The age of the homozygosity by descent segment performed differently in each line, for example F_{HBD} raised 128 generations ago produced a significant positive effect only in the L-Line. The effect of global inbreeding coefficients on the LS was negative in both lines with a higher impact in the H-Line than in the L-Line, suggesting the L-Line having higher robustness. CHR 1, 9, and 13 were candidates for future gene search. In general, more recent F_{ROH} and F_{HBD} presented negative effects on LS while older F_{ROH} and F_{HBD} presented positive effects on LS in both selected lines.

Lay summary

Inbreeding has been defined as the probability that two alleles at any given locus are identical by descent, i.e., both come from a common ancestor. The reduction of fitness in a population due to the levels of inbreeding is known as inbreeding depression (ID). As a result of an experiment of divergent selection for environmental birth weight variability in mice two lines were created: high variability line (H-Line) and low variability line (L-Line). The L-Line outperformed the H-Line in traits related to animal welfare and robustness. In this study we analyzed the impact of inbreeding on the litter size to determine whether there was an ID and whether this ID differently affected the selected lines using pedigree and molecular information. The results obtained suggested that the L-Line presented lower ID. Moreover, the impact of using some molecular inbreeding coefficients was different between lines, despite the same mating restrictions were followed across generations in both lines. These findings could be related to the higher robustness observed in the L-Line.

Key words: divergent experiment, environmental birth weight variability, inbreeding depression, litter size, molecular inbreeding, pedigree inbreeding, robustness

Abbreviations: CHR, autosome; $F_{HBD \geq 12\ Mb}$, genomic inbreeding coefficient obtained from the sum of homozygosity segments equal or greater than 12 Mb; F_{HBD}, genomic inbreeding coefficient obtained from homozygosity by descent probabilities; $F_{HBD \leq 128}$, genomic inbreeding coefficient obtained from homozygosity by descent probabilities less or equal than 64 generations ago; $F_{HBD \leq 16}$, genomic inbreeding coefficient obtained from homozygosity by descent probabilities less or equal than 8 generations ago; $F_{HBD \leq 256}$, genomic inbreeding coefficient obtained from homozygosity by descent probabilities less or equal than 128 generations ago; $F_{HBD \leq 32}$, genomic inbreeding coefficient obtained from homozygosity by descent probabilities less or equal than 16 generations ago; $F_{HBD \leq 4}$, genomic inbreeding coefficient obtained from homozygosity by descent probabilities less or equal than 2 generations ago; $F_{HBD \leq 64}$, genomic inbreeding coefficient obtained from homozygosity by descent probabilities less or equal than 32 generations ago; $F_{HBD \leq 8}$, genomic inbreeding coefficient obtained from homozygosity by descent probabilities less or equal than 4 generations ago; $F_{HBD \geq 128}$, genomic inbreeding coefficient obtained from homozygosity by descent probabilities higher or equal than 64 generations ago; $F_{HBD \geq 16}$, genomic inbreeding coefficient obtained from homozygosity by descent probabilities higher or equal than 8 generations ago; $F_{HBD \geq 256}$, genomic inbreeding coefficient obtained from homozygosity by descent probabilities higher or equal than 128 generations ago; $F_{HBD \geq 32}$, genomic inbreeding coefficient obtained from homozygosity by descent probabilities higher or equal than 16 generations ago; $F_{HBD \geq 4}$, genomic inbreeding coefficient obtained from homozygosity by descent probabilities higher or equal than 2 generations ago; $F_{HBD \geq 64}$, genomic inbreeding coefficient obtained from homozygosity by descent probabilities higher or equal than 32 generations ago; $F_{HBD \geq 8}$, genomic inbreeding coefficient obtained from homozygosity by descent

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probabilities higher or equal than 4 generations ago; F_{HBD128}, genomic inbreeding coefficient obtained from homozygosity by descent probabilities from 64 generations ago; F_{HBD16}, genomic inbreeding coefficient obtained from homozygosity by descent probabilities from 8 generations ago; F_{HBD2}, genomic inbreeding coefficient obtained from homozygosity by descent probabilities from 1 generation ago; F_{HBD256}, genomic inbreeding coefficient obtained from homozygosity by descent probabilities from 128 generations ago; F_{HBD32}, genomic inbreeding coefficient obtained from homozygosity by descent probabilities from 16 generations ago; F_{HBD4}, genomic inbreeding coefficient obtained from homozygosity by descent probabilities from 2 generations ago; F_{HBD512}, genomic inbreeding coefficient obtained from homozygosity by descent probabilities from 256 generations ago; F_{HBD64}, genomic inbreeding coefficient obtained from homozygosity by descent probabilities from 32 generations ago; F_{HBD8}, genomic inbreeding coefficient obtained from homozygosity by descent probabilities from 4 generations ago; $F_{L\&H}$, genomic inbreeding coefficient obtained from the Li and Horvitz matrix; F_{PED}, pedigree inbreeding coefficient; $F_{ROH \geq 16\ Mb}$, genomic inbreeding coefficient obtained from the sum of homozygosity segments equal or greater than 16 Mb; $F_{ROH \geq 2\ Mb}$, genomic inbreeding coefficient obtained from the sum of homozygosity segments equal or greater than 2 Mb; $F_{ROH \geq 20\ Mb}$, genomic inbreeding coefficient obtained from the sum of homozygosity segments equal or greater than 20 Mb; $F_{ROH \geq 26\ Mb}$, genomic inbreeding coefficient obtained from the sum of homozygosity segments equal or greater than 26 Mb; $F_{ROH \geq 32\ Mb}$, genomic inbreeding coefficient obtained from the sum of homozygosity segments equal or greater than 32 Mb; $F_{ROH \geq 8\ Mb}$, genomic inbreeding coefficient obtained from the sum of homozygosity segments equal or greater than 8 Mb; $F_{ROH\ 12\text{-}16\ Mb}$, genomic inbreeding coefficient obtained from the sum of homozygosity segments between 12 and 16 Mb; $F_{ROH\ 16\text{-}20\ Mb}$, genomic inbreeding coefficient obtained from the sum of homozygosity segments between 16 and 20 Mb; $F_{ROH\ 2\text{-}4\ Mb}$, genomic inbreeding coefficient obtained from the sum of homozygosity segments between 2 and 4 Mb; $F_{ROH\ 4\text{-}8\ Mb}$, genomic inbreeding coefficient obtained from the sum of homozygosity segments between 4 and 8 Mb; $F_{ROH\ 4\text{-}8\ Mb}$, genomic inbreeding coefficient obtained from the sum of homozygosity segments between 4 and 8 Mb; $F_{ROH\ 8\text{-}12\ Mb}$, sum of segments between 8 and 12 Mb; F_{ROH}, genomic inbreeding coefficient obtained from runs of homozygosity; $F_{ROH \leq 12\ Mb}$, genomic inbreeding coefficient obtained from the sum of homozygosity segments equal or less than 12 Mb; $F_{ROH \leq 16\ Mb}$, genomic inbreeding coefficient obtained from the sum of homozygosity segments equal or less than 16 Mb; $F_{ROH \leq 20\ Mb}$, genomic inbreeding coefficient obtained from the sum of homozygosity segments equal or less than 20 Mb; $F_{ROH \leq 26\ Mb}$, genomic inbreeding coefficient obtained from the sum of homozygosity segments equal or less than 26 Mb; $F_{ROH \leq 32\ Mb}$, genomic inbreeding coefficient obtained from the sum of homozygosity segments equal or less than 32 Mb; $F_{ROH \leq 4\ Mb}$, genomic inbreeding coefficient obtained from the sum of homozygosity segments equal or less than 4 Mb; $F_{ROH \leq 8\ Mb}$, genomic inbreeding coefficient obtained from the sum of homozygosity segments equal or less than 8 Mb; $F_{ROH \geq 4\ Mb}$, genomic inbreeding coefficient obtained from the sum of homozygosity segments equal or greater than 4 Mb; $F_{ROH1\text{-}2\ Mb}$, genomic inbreeding coefficient obtained from the sum of runs of homozygosity segments between 1 and 2 Mb; $F_{ROH20\text{-}26\ Mb}$, genomic inbreeding coefficient obtained from the sum of homozygosity segments between 20 and 26 Mb; F_{ROHn}, genomic inbreeding coefficient obtained from runs of homozygosity in each autosome, where *n* is the number of the autosome; F_{VR1}, genomic inbreeding coefficient obtained from VanRaden type 1 matrix; F_{VR2}, genomic inbreeding coefficient obtained from VanRaden type 2 matrix; F_{YAN}, genomic inbreeding coefficient obtained from Yang matrix; GRMs, genomic relationship matrices; HBD, homozygosity by descent; H-Line, high variability line; ID, inbreeding depression; L-Line, low variability line; LS, litter size; MAF, minor allele frequency; PCIT, partial correlation coefficients and the information theory methodology; QC, quality control; ROH, runs of homozygosity; RP, reference population; SNPs, single nucleotide polymorphisms.

Introduction

Mating between related individuals leads to an increase in inbreeding, which can have negative effects such as inbreeding depression (ID) (Hedrick and Kalinowski, 2000). ID has been defined as the reduction in the phenotypic mean of a quantitative trait (Falconer, 1996; Leroy, 2014; Ferenčaković et al., 2017). ID has been defined by three hypotheses: partial dominance, over dominance, and epistasis (Kristensen et al., 2010). However, most of the studies concluded that the partial dominance as the primary mechanism (Charlesworth and Charlesworth, 1999; Crow, 1999).

Traditionally, genealogy was used to estimate ID (Leroy, 2014). However, genomic inbreeding coefficients might better capture realized inbreeding when the marker density is large enough (Wang, 2016). Moreover, genomic information is more accurate when the pedigree is incomplete or presents a high incidence of errors. Also, it accounts for Mendelian sampling variation or linkage disequilibrium and could be estimated for a specific region of the genome (Leroy et al., 2013; Leroy, 2014; Pryce et al., 2014; Saura et al., 2015; Wang, 2016; Antonios et al., 2021). Many genomic inbreeding coefficients have been described in the literature, but there is no consensus on which is the most appropriate to estimate identity by descent (Goudet et al., 2018; Villanueva et al., 2021; Arias et al., 2023; Ojeda-Marín et al., 2023a). In fact, different authors have concluded that it would be more appropriate to use certain coefficients or others depending on many factors such as: the objective of study, the effective population size, the demographic history of the population, the marker density or the availability of the allele frequencies of the base population (Alemu et al., 2021; Makanjuola et al., 2020; Villanueva et al., 2021; Caballero et al., 2022; Naji et al., 2024). Some authors showed that only the genomic inbreeding coefficient, that was simply the proportion of SNPs that are homozygous for the individual with ranges between 0 and 1 (Villanueva et al., 2021), was, therefore, consistent with both Malecot's and Wrigth's definition of the inbreeding coefficient when compared to other genomic inbreeding estimators that were obtained from genomic relationship matrices that correct by the allele frequencies in a reference population (Wright, 1931; Malecot, 1948; Villanueva et al., 2021). Moreover, Alemu et al. (2021) showed that measures based on the proportion of genome that is on runs of homozygosity (ROH) or on the excess of homozygosity, better captured the proportion of the genome that was identical by descent. In addition, some studies demonstrated that genomic inbreeding coefficients based on the correlation between uniting gametes or on ROH provide a reliable estimate of ID (Alemu et al., 2021; Caballero et al., 2022).

ROH could be identified through empirical based approaches and model-based approaches (Leutenegger et al., 2003; Druet and Gautier, 2017). In the case of the empirical approaches to detect ROH, the user has to determine the parameters to define a ROH. Moreover, in model-based approaches ROH are modeled as homozygosity by descent (HBD) probabilities along the individual genome (Druet and Gautier, 2017). Both approaches present the possibility of distinguishing between recent and old inbreeding due to the length of the homozygous segments: longer segments are related to recent inbreeding as recombination and mutation had no time to break the segments into smaller segments (McQuillan et al., 2008; Curik et al., 2014; Druet and Gautier, 2017). In terms of fitness, recent inbreeding is related to ID and old inbreeding with the purge phenomena: in the case of recent inbreeding there is not enough time for deleterious alleles to disappear through natural selection (Hinrichs et al., 2007). This particularity allowed other authors to show that longer ROH are more significantly associated with ID in cattle (Doekes et al., 2019; Makanjuola et al., 2020; Naji et al., 2024).

There is no consensus on which genomic inbreeding coefficient better represents identity by descent. One of the approaches most commonly used to determine which

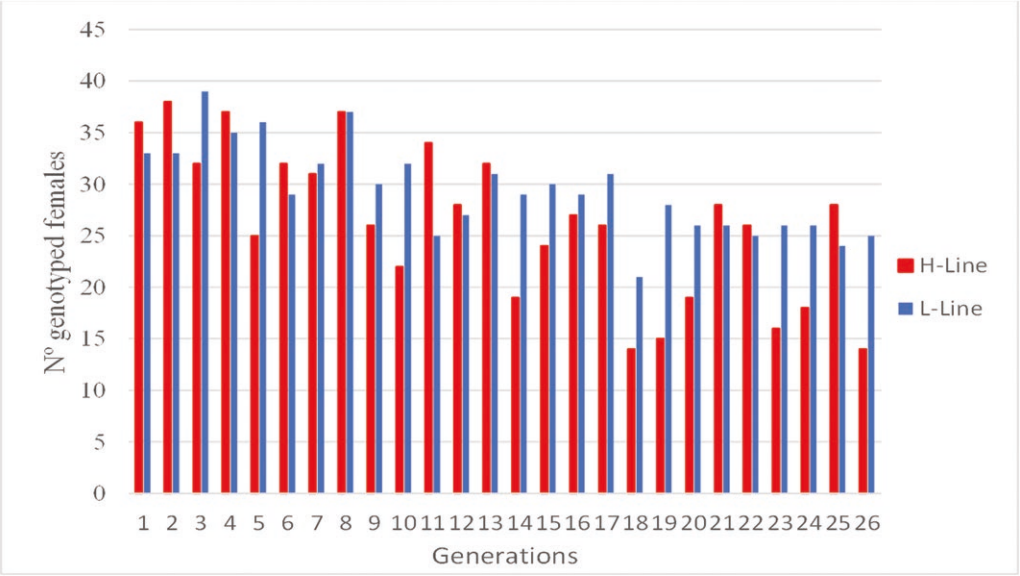

Figure 1. Number of genotyped females in each selection generation of the high variability line (H-Line), and of the low variability line (L-Line) in each selection generation.

coefficient is more representative has been to compare it with the pedigree inbreeding coefficient using Pearson's correlations. The correlations between different inbreeding coefficients estimated using pedigree and genomic information have been broadly provided in the literature (Silió et al., 2013; Rodríguez-Ramilo et al., 2020; Caballero et al., 2022; Arias et al., 2023; Ojeda-Marín et al., 2023a, 2023b). Nevertheless, sometimes a correlation between two inbreeding coefficients (x and y) is spuriously strong because the correlation between a third coefficient (z) is truly high in the cases of xy and yz. Therefore, Reverter and Chan (2008) suggested an approach that combines first-order partial correlation coefficients and the information theory methodology (PCIT) to identify significant associations amongst correlated variables.

An experiment of divergent selection for environmental birth weight variability in mice was successfully developed for 33 generations (Formoso-Rafferty et al., 2016a). As a result of this experiment two lines were created: the high variability line (H-Line) and the low variability line (L-Line). Despite the selection being performed to modify the environmental variance within litter, the effect of selection was observed within and across litters (El-Ouazizi et al., 2023). The individuals from the L-Line showed a better performance in traits related to robustness as overcoming feed restriction and reproductive longevity (Formoso-Rafferty et al., 2019; Formoso-Rafferty et al., 2022). Also, the L-line presented advantages in production, animal welfare and response to selection (Formoso-Rafferty et al., 2016b, 2020). The litter size is directly related to fitness as an individual, which is more likely to leave a genetic legacy in the population if it has more offsprings. The L-Line presented significant greater number of pups born alive than the H-Line despite the fact that there were no significant differences in the ovulation rate between lines (Formoso-Rafferty et al., 2023).

Therefore, the main objective of this study was to estimate differences in ID for litter size in two divergent lines selected for environmental variability for birth weight using pedigree and genomic information.

Material and Methods

Data

In the selection experiment, 43 females were mated with 43 males (one to one) to give each a maximum of two births in each generation. Matings were designed in both lines by optimizing the standard solution that maximizes the genetic response while limiting the kinship with the minimum restriction of not sharing common grandparents: for more details see Formoso-Rafferty et al. (2016a). The housing and management conditions of the animals were in accordance with the Spanish legislation RD 53/2013 on the basic rules for the protection of animals used in experiments and other scientific purposes (Boletín Oficial del Estado, 2013) and approved by the Animal Experimentation Committee (PROEX 224/18).

In total, 1587 females from 26 selection generations (752 of the H-Line and 766 of the L-Line) were genotyped using the Affymetrix Mouse Diversity Genotyping Array which included 616,316 single nucleotide poly morphisms (SNPs). The first generation was used as the reference population (RP) with a total of 70 individuals. Figure 1 shows the number of genotyped females in each selection generation. All the genotyped individuals presented a call rate higher than 97%. The quality control (QC) was applied to the SNPs: 3% of missing genotypes were allowed. In addition, SNPs mapped in sex chromosomes were removed. After applying filtering criteria 545,656 SNPs were retained. This set was used to detect ROH and HBD to ensure maximum genome coverage: a minor allele frequency filter was not applied as pruning for low MAF can ignore large homozygous regions in the genome (Meyermans et al., 2020). In the case of HBD the authors who developed and used the methodology in Druet and Gautier (2017), they concluded that the method accounted for the allele frequencies and, therefore, no filters were needed.

Additional filters were applied to determine the genomic inbreeding estimators derived from the genomic relationship matrices (GRMs): These filters were applied to limit the number of genotyping errors (Weale, 2010). In the SNPs subset described above for ROH and HBD, these filters were not

applied because these methods already account for the possibility of genotyping errors (Druet and Gautier, 2017; Ceballos et al., 2018). SNPs presenting MAFs lower than 0.05 in the reference population were removed. Additionally, remnant SNPs with MAFs less than 0.05 among the whole population were also removed. Finally, 173,546 SNPs were kept.

The pedigree included information from the 26 generations of selection and 5 previous generations containing a total of 5054 individuals, including the 1518 genotyped females.

The litter size (LS), defined as the number of pups born alive, was used from 648 H-Line and 732 L-Line genotyped females.

Inbreeding coefficients

Pedigree inbreeding (F_{PED}), defined as the probability that an individual had two identical alleles by descent, was computed following Meuwissen and Luo (Meuwissen and Luo, 1992). From the genomic data, we started by calculating the genomic inbreeding from GRMs using the nomenclature described by Villanueva et al., (2021): from Li and Horvitz matrix ($F_{L\&H}$) (Li and Horvitz, 1953), from VanRaden type 1 matrix (F_{VR1}) (VanRaden, 2008), from VanRaden type 2 matrix (F_{VR2}) (Leutenegger et al., 2003; VanRaden, 2008), and from Yang matrix (F_{YAN}) (Yang et al., 2010).

Genomic inbreeding based on runs of homozygosity (F_{ROH}) was calculated as in McQuillan et al.(2008). Runs of homozygosity (ROH) were defined as homozygous segments in the individual genome longer than 1 Mb and were detected using sliding windows algorithm with no restrictions in the number of the heterozygotes allowed per ROH only by sliding windows. The parameters were defined following Ojeda-Marín et al. (2023b). They found the highest correlation between F_{PED} and F_{ROH} using this set of parameters for this population. Also, the F_{ROH} were calculated in each autosome as F_{ROHn} where n is the number of each autosome (Ojeda-Marín et al., 2023b).

In addition, F_{ROH} was divided into different coefficients to determine which segments lead to ID and which lead to purge. First, the coefficients were divided into accumulative classes as: $F_{ROH\geq 2\ Mb}$, $F_{ROH\geq 4\ Mb}$, $F_{ROH\geq 8Mb}$, $F_{ROH\geq 12Mb}$, $F_{ROH\geq 16Mb}$, $F_{ROH\geq 20Mb}$, $F_{ROH\geq 26Mb}$ and $F_{ROH\geq 32Mb}$. Second, F_{ROH} were divided into: $F_{ROH\leq 4Mb}$, $F_{ROH\leq 8Mb}$, $F_{ROH\leq 12Mb}$, $F_{ROH\leq 16Mb}$, $F_{ROH\leq 20Mb}$, $F_{ROH\leq 26Mb}$ and $F_{ROH\leq 32Mb}$. Third, F_{ROH} were divided into classes depending on the ROH length: $F_{ROH\ 1\text{-}2\ Mb}$, $F_{ROH\ 2\text{-}4\ Mb}$, $F_{ROH\ 4\text{-}8\ Mb}$, $F_{ROH\ 8\text{-}12\ Mb}$, $F_{ROH\ 12\text{-}16\ Mb}$, $F_{ROH\ 16\text{-}20\ Mb}$, $F_{ROH\ 20\text{-}26\ Mb}$ and $F_{ROH\ 26\text{-}32\ Mb}$.

Finally, genomic inbreeding coefficients were obtained from the probability of the genome to be in a homozygosity-by-descent state (F_{HBD}). This probability was calculated using a 9 HBD classes (k) and 1 non-HBD class (Druet and Gautier 2017). The HBD ratio (R_k) of the k was set at 2, 4, 8, 16, 32, 64, 128, 256, and 512; and the R_k of the non-HBD class was set at 512. The distance in years of the common ancestor was approximately $0.5 \times R_k$. We calculated F_{HBD} as $F_{HBD} = F_{HBD2} + F_{HBD4} + F_{HBD8} + F_{HBD16} + F_{HBD32} + F_{HBD64} + F_{HBD128} + F_{HBD256} + F_{HBD512}$. Moreover, to determine whether the HBD age was related to ID or purge, we divided F_{HBD} into accumulative classes: $F_{HBD\geq 4}$, $F_{HBD\geq 8}$, $F_{HBD\geq 16}$, $F_{HBD\geq 32}$, $F_{HBD\geq 64}$, $F_{HBD\geq 128}$, $F_{HBD\geq 256}$ and $F_{HBD\leq 4}$, $F_{HBD\leq 8}$, $F_{HBD\leq 16}$, $F_{HBD\leq 32}$, $F_{HBD\leq 64}$, $F_{HBD\leq 128}$ and $F_{HBD\leq 256}$.

All the calculated inbreeding coefficients were adjusted by the mean inbreeding of the reference population as described by: Arias et al. (2023) and Ojeda-Marín et al. (2023a, 2023b). Although some coefficients use the frequencies of the reference population to correct the homozygosity detected in the generations analyzed, such as $F_{L\&H}$, F_{VR1}, F_{VR2},and F_{YAN}, correcting by the mean inbreeding coefficient of the reference population reduces the sampling effect.

We used ENDOG v4.8 (Gutierrez and Goyache, 2005) to calculate F_{PED}, our own code to calculate the genomic inbreeding coefficients derived from different GRMs, PLINK v1.9 (Chang et al., 2015) to detect the ROH, and the R package *RzooRoH* (Bertrand et al., 2019) to calculate the HBD probabilities.

Partial correlations

Given the inbreeding coefficients x, y and z, the first order partial correlation coefficients were computed as $r_{xy,z} = \frac{r_{xy} - r_{xz}r_{yz}}{\sqrt{(1-r_{xz}^2)(1-r_{yz}^2)}}$ and the same for $r_{xz,y}$ and $r_{yz,x}$. Hence, $r_{xy,z}$ denotes the strength of the linear relationship between x and y that is independent of z. Then, this partial correlation was compared with the ordinary Pearson's correlation coefficients (r_{xy},r_{xz} and r_{yz}) to see whether the association between two inbreeding coefficients had decreased after eliminating the effect of the third inbreeding coefficient (Reverter and Chan, 2008).

To capture the significant associations for every trio inbreeding coefficient the tolerance level (ε) was calculated as $\varepsilon = \frac{1}{3}\left(\frac{r_{xy,z}}{r_{xy}} + \frac{r_{xz,y}}{r_{xz}} + \frac{r_{yz,x}}{r_{yz}}\right)$. Hence, a correlation between inbreeding coefficients x and y was discarded if $|r_{xy}| \leq |\varepsilon \times r_{xz}|$ *and* $|r_{xy}| \leq |\varepsilon \times r_{yz}|$.

The Pearson correlations, first order partial correlations and the tolerance level were calculated for the following adjusted inbreeding coefficients: F_{PED}, $F_{L\&H}$, F_{VR1}, F_{VR2}, F_{YAN}, F_{ROH}, and F_{HBD} in the H-Line and in the L-Line separately.

The partial correlation coefficients together with the similarity in the tolerance level were calculated with the software PCIT (Watson-Haigh et al., 2010). The visualization of the significant networks between the inbreeding coefficients were performed using the software Cytoscape v 3.10.1 (Shannon et al., 2003).

Inbreeding depression analysis

The ID analyses were performed as the linear regression coefficient of the LS of individuals on their different adjusted inbreeding coefficients and the age of the female at birth in days and the female's mother litter size were included as continuous fixed effects. The ID analyses were computed separately in each line. The ID analyses were performed in six blocks: the first block was calculated with the global inbreeding coefficients calculated with pedigree and genomic information. The second block was calculated using F_{ROH} on each chromosome. The third block was estimated using F_{ROH} calculated by the length of the ROH segments. The fourth block was estimated using F_{HBD} age related classes. The fifth block was estimated using F_{ROH} accumulative length classes. Finally, the sixth block of ID analyses was estimated using accumulative F_{HBD} classes. In the second, third and fourth blocks, all inbreeding coefficients were included in the equation as part of the same analysis. In the case of the second and third blocks, this was because we assumed that total F_{ROH} was composed of all chromosomal F_{ROH} and all F_{ROH} of different lengths. In the case of the fourth block, the same criterion was assumed as the total F_{HBD} was calculated from different age-related HBD classes.

To obtain the significance of the regression coefficients with the different inbreeding coefficients we applied a Bonferroni

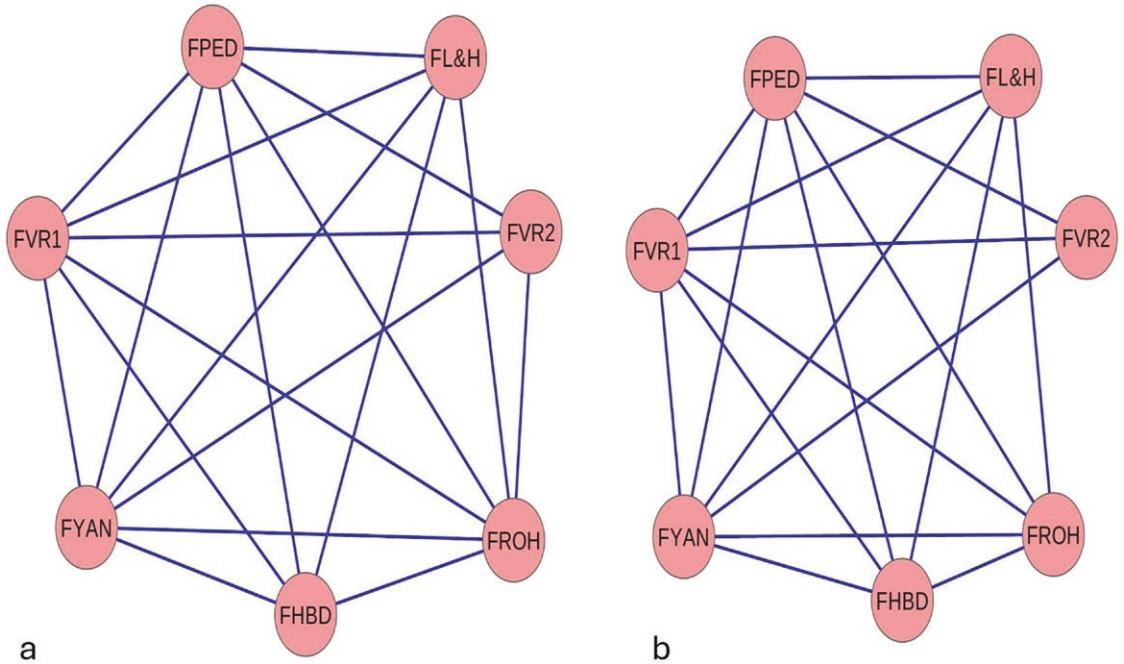

Figure 2. Network of significant associations obtained from PCIT for different inbreeding estimates adjusted by the respective mean inbreeding in reference population. (a) Network of the high variability line. (b) Network of the low variability line. F_{PED}: pedigree inbreeding coefficient. $F_{L\&H}$: inbreeding coefficient derived from the Li and Horvitz genomic matrix. F_{VR1}: inbreeding coefficient derived from VanRaden's type 1 genomic matrix. F_{VR2}: inbreeding coefficient derived from VanRaden type 2 genomic matrix. F_{YAN}: inbreeding coefficient derived from Yang genomic matrix. F_{ROH}: inbreeding coefficient obtained from runs of homozygosity. F_{HBD} inbreeding coefficient obtained from homozygosity by descent probabilities.

correction in some blocks of analysis. Therefore, in the first block a regression coefficient was considered significant if p was lower than 0.05/14, in the fifth and sixth block of analysis a regression coefficient was considered significant if P was lower than 0.05/28. In each Bonferroni correction the denominator was calculated as the number of inbreeding regression coefficients in each block of analysis multiplied by two; one for each selected line. The second, the third and the fourth blocks of analyses Bonferroni correction was not applied because each block was compounded by a single analysis.

The linear regression analysis was performed using the function "lm" of the stats R package (R Core Team, 2013).

Results

The Pearson correlations and the tolerance level between the inbreeding coefficients are shown in Supplementary Table S1. The correlations between the following pairs were not significant in the H-Line: $F_{L\&H}$-F_{VR2}, F_{HBD}-F_{VR2}. In the L-Line the correlations among $F_{L\&H}$-F_{VR2}, F_{HBD}-F_{VR2}, and F_{ROH}-F_{VR2} were not significant. The rest of the correlations were significant and positive: between 0.84 (F_{PED}-F_{VR1} and F_{PED}-F_{VR2}) and 0.98 ($F_{L\&H}$-F_{ROH}, $F_{L\&H}$-F_{HBD}, F_{VR1}-F_{VR2}, and F_{VR1}-F_{YAN}) in the H-Line and between 0.83 (F_{PED}-F_{VR1} and F_{PED}-F_{VR2}) and 0.98 ($F_{L\&H}$-F_{ROH}, $F_{L\&H}$-F_{HBD}, and F_{VR1}-F_{VR2}) in the L-Line. Figure 2 shows the network between the coefficients in both lines. The F_{PED}, F_{YAN}, and F_{VR1} presented statistically significant correlations with all the rest of the coefficients having six edges each in both lines. In the H-Line (Figure 2a) F_{ROH} also presented six edges with the rest of inbreeding coefficients.

Table 1 shows the regression coefficients of the different inbreeding coefficients adjusted by the respective mean inbreeding coefficients of the reference population and the significance. In the H-Line the values of the regression coefficients obtained from genomic data were between −3.71 with F_{VR2} and −5.09 with F_{HBD}. The regression coefficient of F_{PED} in the H-Line was −5.67. In the H-Line, the ID effects of the maximum F_{VR2}, F_{HBD}, and F_{PED} in the LS were −2.03, −1.77 and −1.75 pups, respectively. In the L-Line the regression coefficients obtained from genomic data were between −3.52 with F_{VR2} and −4.55 with F_{HBD}. The regression coefficient of F_{PED} in the L-Line was −4.08. In this line, the ID effects of the maximum F_{VR2}, F_{HBD}, and F_{PED} in the LS were −1.83, −1.67, and −1.23 pups, respectively. All the regression coefficients of the inbreeding coefficients were significant after the Bonferroni correction in both lines. Moreover, all the regression coefficients were lower in the H-Line than in the L-Line. However, only F_{PED} presented a statistically significant difference between lines ($P \leq 0.05$).

Table 2 shows the regression coefficients per chromosome in both selected lines calculated using ROH. In the H-Line only F_{ROH13} produced a significant negative effect in the LS, the regression coefficient was −1.17 and the ID effect of maximum F_{ROH13} in LS was −0.85 pups. In the L-Line F_{ROH1} (−1.68) and F_{ROH9} (−0.92) presented a significant negative effect in the LS with $P \leq 0.05$. In this line, the effect of the maximum F_{ROH1} and F_{ROH9} in the LS was −1.21 and −0.67 pups, respectively. Differences between lines were observed in all the autosomes with a significance of $P \leq 0.05$ except in autosomes 4, 9, 14, and 19. In autosomes 1, 7, 8, 9, and 16 the regression coefficient of chromosomic F_{ROH} was negative in both lines. In autosomes 3, 5, 6, 11, 12, 13, 15, 17 and 18 the regression coefficient of chromosomic F_{ROH} was negative in one of the lines and positive in the other. Finally, only in the autosome 2 was this coefficient positive in both lines. The mother's litter size was significant in the L-Line with $P \leq 0.05$ being −0.09.

Table 1. Estimates of inbreeding depression for litter size at the first birth in high variability line (H-Line) and low variability line (L-Line).

H-Line	m_inb	m_age	m_mls	effect min	effect max
F_{PED}	-5.67*[a]	-0.01	−0.02	0.22	−1.75
$F_{L\&H}$	−4.43*	−0.01	−0.01	0.80	−2.01
F_{VR1}	−4.49*	−0.01	−0.01	0.61	−2.11
F_{VR2}	−3.71*	−0.01	−0.01	0.59	−2.03
F_{YAN}	−4.55*	−0.01	−0.01	0.70	−2.29
F_{ROH}	−4.70*	−0.01	−0.01	0.70	−1.99
F_{HBD}	−5.09*	−0.01	−0.01	0.90	−1.77
L–Line	**m_inb**	**m_age**	**m_mls**	**effect min**	**effect max**
F_{PED}	−4.08*[b]	−0.01	−0.09	−0.12	−1.23
$F_{L\&H}$	−4.06*	−0.01	−0.08	0.37	−1.63
F_{VR1}	−4.21*	−0.01	−0.09	0.21	−1.84
F_{VR2}	−3.52*	−0.01	−0.09	0.19	−1.83
F_{YAN}	−4.22*	−0.01	−0.09	0.21	−1.76
F_{ROH}	−4.47*	−0.01	−0.09	0.35	−1.73
F_{HBD}	−4.55*	−0.01	−0.09	0.39	−1.67

m_inb: inbreeding regression coefficient. m_age: regression coefficient of the age of the female at birth. m_mls: regression coefficient of the female's mother litter size. effect min: effect of each minimum inbreeding coefficient on the litter size. effect max: effect of each maximum inbreeding coefficient on the litter size. F_{PED}: pedigree inbreeding coefficient. $F_{L\&H}$: inbreeding coefficient derived from the Li and Horvitz genomic matrix. F_{VR1}: inbreeding coefficient derived from VanRaden type 1 genomic matrix. F_{VR2}: inbreeding coefficient derived from VanRaden type 2 genomic matrix. F_{YAN}: inbreeding coefficient derived from Yang's genomic matrix. F_{ROH}: inbreeding coefficient obtained from runs of homozygosity. F_{HBD}: inbreeding coefficient obtained from homozygosity by descent probabilities.
*: significant after Bonferroni correction in each selected line.
[a, b]differences between lines significant with $p \leq 0.05$.

The results for the ID analysis by the length of the ROH segment are shown in Table 3. In the H-Line only the longest segments ($F_{ROH\geq32Mb}$) produced a significant decrease of LS with a $P \leq 0.05$. In this line, the regression coefficient of $F_{ROH\geq32Mb}$ was −8.06 and the ID effect of the maximum $F_{ROH\geq32Mb}$ in the LS was −1.51 pups. In the L-Line $F_{ROH8\text{-}12Mb}$ (−12.32) and $F_{ROH16\text{-}20Mb}$ (−11.11) there was a significant decrease of LS with $P \leq 0.05$. The ID effect of the maximum $F_{ROH8\text{-}12Mb}$ and $F_{ROH16\text{-}20Mb}$ in the LS was −1.04 and −0.84 pups in the L-Line, respectively. The mother's litter size was significantly negative with $P \leq 0.05$ in the H-Line (−0.09). Significant differences between lines were detected in all the inbreeding coefficients except in $F_{ROH16\text{-}20Mb}$. Moreover, the age of birth and the mother litter size were also significantly different between lines. The descriptive statistics of all the inbreeding coefficient used in the present analysis are shown in Supplementary Table S2. The standard deviation (SD) of F_{ROH} obtained from different length segments was greater when the length of the used segments increased in both selected lines, i.e., younger segments presented greater SD.

Table 4 shows the ID analysis performed with F_{HBD} calculated from different HBD age probability. There was no significant effect of any of F_{HBD} from different origin generation in the H-Line. Nevertheless, in the L-line F_{HBD8} resulted in a significant negative effect (−6.94) and F_{HBD256} resulted positive (28.42) with a $P \leq 0.05$. In this line, the ID effect of the maximum F_{HBD8} and F_{HBD256} in the LS was −2.52 and 1.65 pups, respectively. Moreover, significant differences between lines were detected in all age related F_{HBD} and in the mother litter size with $P \leq 0.05$. Similar to what was observed for the ROH segments, younger classes had greater SD than older classes in both selected lines (Supplementary Table S2).

Table 5 shows the ID analysis in both selected lines using accumulative F_{ROH} coefficients. When $F_{ROH\geq2Mb}$ to $F_{ROH\geq26Mb}$ were used, the regression coefficient was lower when only longer segments were fitted. In the H-Line the slopes were between −5.03 with $F_{ROH\geq2\ Mb}$ to −7.86 with $F_{ROH\geq26Mb}$, and in the L-Line they were between −4.55 with $F_{ROH\geq2\ Mb}$ to −6.27 with $F_{ROH\geq26Mb}$. In both lines, the effect of the maximum accumulative F_{ROH} in the LS was more negative when most of the segments conformed to F_{ROH} than when only the longest segments conformed to F_{ROH}. All these inbreeding regression coefficients were significant after the Bonferroni correction in both lines. When F_{ROH} was calculated using shorter segments ($F_{ROH\leq32Mb}$ to $F_{ROH\leq4Mb}$), the inbreeding regression coefficients were greater when shorter segments were used: in the H-Line these were between −3.53 with $F_{ROH\leq32Mb}$ to 21.94 with $F_{ROH\leq4Mb}$. In the L-Line these were between −3.38 with $F_{ROH\leq32Mb}$ to 20.07 with $F_{ROH\leq4Mb}$. In the H-Line the regression coefficient of $F_{ROH\leq4Mb}$ was statistically significant, with a maximum effect in the LS of 0.95 pups more, while in the L-Line both $F_{ROH\leq8Mb}$ and $F_{ROH\leq4Mb}$ were statistically significant. In this line the effect of the maximum $F_{ROH\leq8Mb}$ and $F_{ROH\leq4Mb}$ in the LS was 1.10 and 0.97 pups more, respectively. No significant differences between lines were detected in this block of analysis.

The ID analyses performed using accumulative F_{HBD} are shown in Table 6. When $F_{HBD\leq4}$ to $F_{HBD\leq256}$ were used, all the obtained regression coefficients were negative: in the H-Line these were between −2.00 with $F_{HBD\leq8}$ and −5.41 with $F_{HBD\leq4}$. However, in the H-Line the inbreeding regression coefficients were significant between $F_{HBD\leq16}$ (-4.27) and $F_{HBD\leq256}$ (−4.83). In the L-Line the inbreeding regression coefficients for accumulative F_{HBD} were between -0.82 with $F_{HBD\leq4}$ and −4.10 with $F_{HBD\leq256}$. In this line, the inbreeding regression coefficients were significant between $F_{HBD\leq8}$ (−3.42) and $F_{HBD\leq256}$ (−4.10). When F_{HBD} was calculated backwards, i.e., using

Table 2. Estimates of inbreeding depression for litter size at the first birth in high variability line (H–Line) and low variability line (L–Line), using genomic inbreeding obtained from runs of homozygosity (F_{ROH}) in each autosome adjusted by the mean F_{ROH} in each autosome in the reference population.

	H–line			L–line		
	m	effect min	effect max	m	effect min	effect max
F_{ROH1}	−0.70[a]	0.38	−0.44	−1.68*[b]	0.81	−1.21
F_{ROH2}	0.38[a]	−0.06	0.39	0.49[b]	0.00	0.56
F_{ROH3}	−0.84[a]	0.43	−0.69	0.11[b]	0.21	0.34
F_{ROH4}	−0.86	0.50	−0.46	−0.93	0.42	−0.53
F_{ROH5}	−0.65[a]	0.48	−0.30	0.22[b]	0.16	0.39
F_{ROH6}	0.13[a]	0.32	0.47	−0.44[b]	0.18	−0.31
F_{ROH7}	−0.38[a]	0.30	−0.12	−0.13[b]	0.19	0.05
F_{ROH8}	−0.02[a]	0.20	0.18	−0.10[b]	0.10	−0.03
F_{ROH9}	−0.34[a]	0.25	−0.20	−0.92*[b]	0.51	−0.67
F_{ROH10}	−0.48	0.38	−0.29	−0.54	0.33	−0.35
F_{ROH11}	0.33[a]	−0.18	0.35	−0.80[b]	0.42	−0.51
F_{ROH12}	−0.67[a]	0.45	−0.43	0.19[b]	0.18	0.40
F_{ROH13}	−1.17*[a]	0.76	−0.85	0.20[b]	0.08	0.31
F_{ROH14}	0.1	0.08	0.22	0.09	−0.05	0.09
F_{ROH15}	0.54[a]	−0.22	0.70	−0.17[b]	0.14	−0.16
F_{ROH16}	−0.41[a]	0.39	−0.22	−0.04[b]	0.18	0.13
F_{ROH17}	0.09[a]	0.12	0.24	−0.35[b]	0.30	−0.11
F_{ROH18}	−0.28[a]	0.25	−0.12	0.15[b]	0.11	0.29
F_{ROH19}	0.04	0.19	0.24	0.06	0.09	0.17
Age of birth	−0.01			−0.01		
mls	0.00[a]			−0.09*[b]		

m: inbreeding regression coefficient. effect min: effect of each minimum inbreeding coefficient on the litter size. effect max: effect of each maximum inbreeding coefficient on the litter size. mls: female's mother litter size. F_{ROHx}: F_{ROH} in each autosome where x is the number of the chromosome.
*: significant with $p \leq 0.05$ in each selected line.
[a, b]: differences between lines significant with $p \leq 0.05$.

Table 3. Estimates of inbreeding depression for litter size at the first birth in high variability line (H-Line) and low variability line (L-Line) using genomic inbreeding obtained from runs of homozygosity (F_{ROH}) of different lengths.

	H-Line			L-Line		
	m	effect min	effect max	m	effect min	effect max
$F_{ROH\geq32Mb}$	−8.06*[a]	0.33	−1.51	−4.96[b]	0.21	−1.19
$F_{ROH26-32Mb}$	−11.59[a]	0.21	−1.15	−3.39[b]	0.07	−0.25
$F_{ROH20-26Mb}$	−4.55[a]	0.15	−0.40	−5.70[b]	0.17	−0.56
$F_{ROH16-20Mb}$	−11.38	0.44	−0.81	−11.11*	0.43	−0.84
$F_{ROH12-16Mb}$	−3.07[a]	0.16	−0.20	−6.41[b]	0.21	−0.44
$F_{ROH8-12Mb}$	−7.15[a]	0.49	−0.48	−12.32*[b]	0.47	−1.04
$F_{ROH4-8Mb}$	−9.64[a]	0.56	−0.57	6.52[b]	−0.33	0.36
$F_{ROH2-4Mb}$	−9.74[a]	0.49	−0.31	2.29[b]	−0.07	0.09
$F_{ROH1-2Mb}$	17.39[a]	−0.53	0.28	0.20[b]	−0.01	0.00
Age of birth	−0.01[a]			−0.01[b]		
Mls	−0.01[a]			−0.09*[b]		

m: inbreeding regression coefficient. effect min: effect of each minimum inbreeding coefficient on the litter size. effect max: effect of each maximum inbreeding coefficient on the litter size. F_{ROH1}-2 *Mb*: sum of segments between 1 and 2 Mb. F_{ROH} *2-4 Mb*: segments between 2 and 4 Mb. $F_{ROH\ 4\text{-}8\ Mb}$: sum of segments between 4 and 8 Mb. $F_{ROH\ 4\text{-}8\ Mb}$: sum of segments between 4 and 8 Mb. $F_{ROH\ 8\text{-}12\ Mb}$: sum of segments between 8 and 12 Mb. $F_{ROH\ 12\text{-}16\ Mb}$: sum of segments between 12 and 16 Mb. $F_{ROH\ 16\text{-}20\ Mb}$: sum of segments between 16 and 20 Mb. $F_{ROH\ 20\text{-}26\ Mb}$: sum of segments between 20 and 26 Mb. $F_{ROH\ \geq32\ Mb}$: sum of segments equal or greater than 32 Mb.
*: significant with $p \leq 0.05$ in each selected line.
[a, b]: differences between lines significant with $p \leq 0.05$.

Table 4. Estimates of inbreeding depression for litter size at first birth in high variability line (H-Line) and low variability line (L-Line) using genomic inbreeding derived from homozygosity by descent probabilities adjusted by the mean inbreeding coefficient of the reference population (F_{HBD}) of different generations of ancestors.

	H-Line			L-Line		
	m	effect min	effect max	m	effect min	effect max
F_{HBD2}	−7.66[a]	0.03	−1.35	−9.63[b]	0.04	−1.89
F_{HBD4}	−6.70[a]	0.09	−1.84	−4.38[b]	0.07	−1.75
F_{HBD8}	−3.26[a]	0.20	−1.40	−6.94*[b]	0.31	−2.52
F_{HBD16}	−3.83[a]	0.59	−1.57	−4.90[b]	0.74	−1.64
F_{HBD32}	−0.26[a]	0.03	−0.08	−3.73[b]	0.53	−1.14
F_{HBD64}	2.60[a]	−0.40	0.27	0.17[b]	−0.06	−0.02
F_{HBD128}	6.76[a]	−0.07	1.16	3.38[b]	−0.02	0.74
F_{HBD256}	19.50[a]	0.00	1.13	28.42*[b]	0.00	1.65
F_{HBD512}	25.67[a]	−0.86	0.28	4.87[b]	−0.18	0.02
Age of birth	−0.01			−0.01		
Mls	−0.01[a]			−0.09*[b]		

m: inbreeding regression coefficient. effect min: effect of each minimum inbreeding coefficient on the litter size. effect max: effect of each maximum inbreeding coefficient on the litter size. mls: mother litter size. F_{HBD2}: 1 generation ago. F_{HBD4}: 2 generations ago. F_{HBD8}: 4 generations ago. F_{HBD16}: 8 generations ago. F_{HBD32}: 16 generations ago. F_{HBD64}: 32 generations ago. F_{HBD128}: HBD 64 generations ago. F_{HBD256}: 128 generations ago. F_{HBD512}: 256 generations ago.
*: significant with $p \leq 0.05$ in each selected line.
[a, b]: differences between lines significant with $p \leq 0.05$.

Table 5. Estimates of inbreeding depression for litter size at the first birth in high variability line (H-Line) and low variability line (L-Line) using genomic inbreeding obtained from runs of homozygosity (F_{ROH}) of different accumulative lengths.

	H-Line					L-Line				
	m_inb	m_age	m_mls	effect min	effect max	m_inb	m_age	m_mls	effect min	effect max
$F_{ROH\geq 26\ Mb}$	−7.86*	−0.01	−0.01	0.48	−1.82	−6.27*	−0.01	−0.08	0.31	−1.74
$F_{ROH\geq 20\ Mb}$	−6.87*	−0.01	−0.01	0.52	−1.81	−6.01*	−0.01	−0.08	0.37	−1.95
$F_{ROH\geq 16\ Mb}$	−6.69*	−0.01	−0.01	0.59	−1.99	−6.14*	−0.01	−0.09	0.46	−1.97
$F_{ROH\geq 12\ Mb}$	−5.91*	−0.01	−0.01	0.68	−1.87	−5.86*	−0.01	−0.09	0.46	−2.12
$F_{ROH\geq 8\ Mb}$	−5.47*	−0.01	−0.01	0.78	−1.97	−5.71*	−0.01	−0.09	0.58	−2.11
$F_{ROH4\geq\ Mb}$	−5.21*	−0.01	−0.01	0.72	−2.06	−4.75*	−0.01	−0.09	0.39	−1.79
$F_{ROH\geq 2\ Mb}$	−5.03*	−0.01	−0.01	0.71	−2.08	−4.55*	−0.01	−0.09	0.34	−1.76
$F_{ROH\leq 32\ Mb}$	−3.53	−0.01	0.02	0.69	−1.01	−3.38	−0.01	−0.07	0.44	−1.00
$F_{ROH\leq 26\ Mb}$	−1.27	−0.01	0.02	0.23	−0.32	−2.08	−0.01	−0.06	0.33	−0.52
$F_{ROH\leq 20\ Mb}$	0.46	−0.01	0.02	−0.09	0.10	−0.26	−0.01	−0.06	0.03	−0.05
$F_{ROH\leq 16\ Mb}$	3.9	−0.01	0.01	−0.72	0.61	3.66	−0.01	−0.07	−0.41	0.84
$F_{ROH\leq 12\ Mb}$	5.95	−0.01	0.01	−1.14	0.57	6	−0.01	−0.08	−0.55	1.09
$F_{ROH\leq 8\ Mb}$	8.31	−0.01	0	−1.14	0.65	13.46*	−0.01	−0.1	−0.85	1.10
$F_{ROH\leq 4\ Mb}$	21.94*	−0.01	−0.01	−1.67	0.95	20.07*	−0.01	−0.08	−0.70	0.97

m_inb: inbreeding regression coefficient. m_age: regression coefficient of the age of the female at birth. m_mls: regression coefficient of the female's mother litter size. effect min: effect of each minimum inbreeding coefficient on the litter size. effect max: effect of each maximum inbreeding coefficient on the litter size. $F_{ROH\geq 2\ Mb}$: sum of segments equal or greater than 2 Mb. $F_{ROH\geq 4\ Mb}$: sum of segments equal or greater than 4 Mb. $F_{ROH\geq 8\ Mb}$: sum of segments equal or greater than 8 Mb. $F_{HBD\geq 12\ Mb}$: sum of segments equal or greater than 12 Mb. $F_{ROH\geq 16\ Mb}$: sum of segments equal or greater than 16 Mb. $F_{ROH\geq 20\ Mb}$: sum of segments equal or greater than 20 Mb. $F_{ROH\geq 26\ Mb}$: sum of segments equal or greater than 26 Mb. $F_{ROH\leq 32\ Mb}$: sum of segments equal or less than 32 Mb. $F_{ROH\leq 26\ Mb}$: sum of segments equal or less than 26 Mb. $F_{ROH\leq 20\ Mb}$: sum of segments equal or less than 20 Mb. $F_{ROH\leq 16\ Mb}$: sum of segments equal or less than 16 Mb. $F_{ROH\leq 12\ Mb}$: sum of segments equal or less than 12 Mb. $F_{ROH\leq 8\ Mb}$: sum of segments equal or less than 8 Mb. $F_{ROH\leq 4\ Mb}$: sum of segments equal or less than 4 Mb.
*: significant after Bonferroni correction in each selected line.

probabilities belonging to more and more distant ancestors ($F_{HBD\geq 4}$ to $F_{HBD\geq 256}$), in the H-Line the regression coefficients were between −4.27 with $F_{HBD\geq 4}$ to 28.66 with $F_{HBD\geq 256}$. Nevertheless, only $F_{HBD\geq 4}$(−4.27), $F_{HBD\geq 32}$ (4.00) and $F_{HBD\geq 256}$ (28.66) were statistically significant. In the L-Line inbreeding regression coefficients values when F_{HBD} was calculated backwards were between −3.91 with $F_{HBD\geq 4}$ to 32.23 with $F_{HBD\geq 256.}$ In the case of the L-Line, only $F_{HBD\geq 4}$ (−3.91), $F_{HBD\geq 8}$ (−2.68) and $F_{HBD\geq 256}$ (32.23) were statistically significant. Significant differences with $P \leq 0.05$ between lines were detected for $F_{HBD\geq 16}$ and $F_{HBD\geq 32}$. In this block of analysis, the effect of the maximum inbreeding coefficient in the LS was not always

Table 6. Estimates of inbreeding depression for litter size at the first birth in high variability line (H-Line) and low variability line (L-Line) using genomic inbreeding obtained from homozygosity by descent probabilities (F_{HBD}) of different accumulative age classes.

	H-Line					L-Line				
	m_inb	m_age	m_mls	effect min	effect max	m_inb	m_age	m_mls	effect min	effect max
$F_{HBD\leq4}$	−5.41	0	0.01	0.10	−1.47	−0.82	−0.01	−0.06	0.04	−0.30
$F_{HBD\leq8}$	−2	−0.01	0.01	0.21	−0.78	−3.42*	−0.01	−0.08	0.27	−1.21
$F_{HBD\leq16}$	−4.27*	−0.01	0	1.07	−1.82	−3.22*	−0.01	−0.09	0.67	−1.22
$F_{HBD\leq32}$	−3.50*	−0.01	−0.01	0.77	−1.42	−3.32*	−0.01	−0.08	0.53	−1.39
$F_{HBD\leq64}$	−4.41*	−0.01	0.00	1.22	−1.52	−3.62*	−0.01	−0.06	0.81	−1.16
$F_{HBD\leq128}$	−3.41*	−0.01	−0.01	0.88	−1.90	−3.11*	−0.01	−0.08	0.41	−1.37
$F_{HBD\leq256}$	−4.83*	−0.01	−0.01	0.74	−1.93	−4.10*	−0.01	−0.09	0.28	−1.59
$F_{HBD\geq4}$	−4.27*	−0.01	−0.01	1.04	−1.61	−3.91*	−0.01	−0.08	0.72	−1.44
$F_{HBD\geq8}$	−1	−0.01	0.02	0.36	−0.31	−2.68*	−0.01	−0.07	0.53	−0.87
$F_{HBD\geq16}$	−0.26[a]	−0.01	0.02	0.05	−0.15	1.49[b]	−0.01	−0.07	−0.53	0.29
$F_{HBD\geq32}$	4.00*[a]	−0.01	0.01	−1.31	0.82	1.64[b]	−0.01	−0.07	−0.35	0.39
$F_{HBD\geq64}$	3.19	−0.01	0.01	−0.52	0.38	2.97	−0.01	−0.07	−0.44	0.33
$F_{HBD\geq128}$	−5.01	−0.01	0.02	0.24	−0.78	−1.43	−0.01	−0.06	0.05	−0.32
$F_{HBD\geq256}$	28.66*	−0.01	0.00	−0.97	0.75	32.23*	−0.01	−0.07	−1.07	1.13

m_inb: inbreeding regression coefficient. m_age: regression coefficient of the age of the female at birth. m_mls: regression coefficient of the female's mother litter size. effect min: effect of each minimum inbreeding coefficient on the litter size. effect max: effect of each maximum inbreeding coefficient on the litter size. $F_{HBD\leq4}$: sum of homozygosity by descent probabilities (HBD) less or equal than 2 generations ago. $F_{HBD\leq8}$: sum of HBD less or equal than 4 generations ago. $F_{HBD\leq16}$: sum of HBD less or equal than 8 generations ago. $F_{HBD\leq32}$: sum of HBD less or equal than 16 generations ago. $F_{HBD\leq64}$: sum of HBD less or equal than 32 generations ago. $F_{HBD\leq128}$: sum of HBD less or equal than 64 generations ago. $F_{HBD\leq256}$: sum of HBD less or equal than 128 generations ago. $F_{HBD\geq4}$: sum of HBD higher or equal than 2 generations ago. $F_{HBD\geq8}$: sum of HBD higher or equal than 4 generations ago. $F_{HBD\geq16}$: sum of HBD higher or equal than 8 generations ago. $F_{HBD\geq32}$: sum of HBD higher or equal than 16 generations ago. $F_{HBD\geq64}$: sum of HBD higher or equal than 32 generations ago. $F_{HBD\geq128}$: sum of HBD higher or equal than 64 generations ago. $F_{HBD\geq256}$: sum of HBD higher or equal than 128 generations ago.
*: significant after Bonferroni correction in each selected line.
[a, b]differences between lines significant with $p \leq 0.05$.

negative when most of the age classes were used to calculate accumulative F_{HBD}.

Discussion

In livestock species, most breeds have a limited number of individuals. This can lead to mating between relatives. As a result, some breeders need to control the increase in inbreeding that could result in ID (Leroy, 2014). Inbreeding, and in turn ID, has traditionally been addressed from pedigree. However, if the pedigree is not available or complete, molecular information provides a solution. This population of divergently selected mice for environmental birth weight variability is useful to study the effects of different inbreeding coefficients calculated from different sources of information on a reproductive trait such as LS. This is a population with discrete generations subjected to equal selection intensity, but in the opposite direction. Also, the mating design was exactly the same in both lines: at least the crossing pairs were prevented from sharing grandparents (Formoso-Rafferty et al., 2016a). Therefore, from the point of view of inbreeding evolution, the two lines behaved as replicates of the same mating system. Hence, the observed differences were due to the correlated response to environmental variability. Other studies performed in this population concluded that there were no differences in global inbreeding between lines (Ojeda-Marín et al., 2023a, 2023b). This refuted the hypothesis that selection for homogeneity resulted in more homozygous individuals (Lewontin, 1964; Zhivotovsky, 1992). Therefore, the aim of the present analysis was to determine whether, despite the same overall level of inbreeding in the two lines, there were differences in inbreeding depression on litter size in the selected lines.

When the global inbreeding coefficients relationships were studied using the PCIT algorithm in these lines, the most representative coefficients were F_{PED}, F_{YAN}, F_{VR1} and $F_{ROH,}$ because these coefficients presented the greatest number of significant correlations with the other coefficients. These inbreeding coefficients are based on different constrains: F_{PED} is completely defined in probability terms (Malecot, 1948); F_{VR1} (VanRaden, 2008) provides a value relative to allele frequencies in the reference population; F_{YAN} (Yang et al., 2010) also provides a value relative to allele frequencies in a reference population and was designed to give more weight in rare alleles; and F_{ROH} (McQuillan et al., 2008) was calculated from an empirical approach that measures the proportion of the genome in long stretches of homozygote sites. This demonstrates the robustness of the pedigree and genomic information obtained from the divergent selection experiment from different sources. The fact that F_{VR2}, gave more weight in the SNPs of low frequency (VanRaden et al., 2011), led to a non significant correlation with $F_{L\&H}$ and F_{HBD}. This can be explained by the constraints on the definition of these inbreeding coefficients that are more flexible in the way that the population SNPs frequencies influence their performance (Alemu et al., 2021; Caballero et al., 2022). Moreover, the differences in the correlation between F_{ROH} and F_{VR2} in the selected lines could be explained by the different distribution of F_{ROH} in each chromosome, already described in this population (Ojeda-Marín et al., 2023b). Furthermore, the results of this study, together with those obtained in previous studies in this population, suggested that the differences between lines in the overall performance of the

inbreeding coefficients would not explain the differences in performance between the selected lines (Ojeda-Marín et al., 2023a, 2023b).

Other authors analyzed the effect of inbreeding on the LS in other prolific species such as pigs (Farkas et al., 2007; Silió et al., 2013; Casellas et al., 2019; Hervás-Rivero et al., 2023), rabbits (Ragab et al., 2015), dogs (Leroy et al., 2015) and other mice populations (Hinrichs et al., 2007). These studies used different information, but most of them were only based on pedigree information (Farkas et al., 2007; Hinrichs et al., 2007; Leroy et al., 2015; Ragab et al., 2015; Casellas et al., 2019). The results of the effect of inbreeding in these studies were different; some of them split the F_{PED} in different coefficients in function of the distance from the common ancestors (Hinrichs et al., 2007; Silió et al., 2013; Ragab et al., 2015) and showed that inbreeding produced by recent pedigree ancestors led to a negative impact on litter size in some populations. Also in dogs (Leroy et al., 2015) the effect of global F_{PED} was negative on litter size. In the present study, the global genomic and pedigree inbreeding effect on the LS was negative in both selected lines. Moreover, in both selected lines the phenotypic trend (Supplemental Material, Figure S1) was negative across generations. Therefore, the increase of inbreeding across generations resulted in ID effect in both selected lines. However, our results suggest that the selection for low variability of birth weight resulted in a lower ID: at the maximum value of F_{PED} ID effect resulted in −1.75 pups in the H-Line and in −1.23 pups in the L-Line. Moreover, using genomic information, for example, at the maximum value of F_{HBD} ID effect resulted in −1.77 pups in the H-Line and -1.67 pups in the L-Line. Previous studies of this mice population showed that the L-Line performed better for LS (Formoso-Rafferty et al., 2016b).

Other authors reported that the regression coefficient of F_{PED} was not significant while the regression coefficient of genomic inbreeding coefficients was significant (Naji et al., 2024). In the mice selected lines, F_{PED} presented similar significance than the genomic inbreeding coefficients. Other studies performed in the population of mice divergently selected for birth weight variability showed high correlations between F_{PED} and the genomic coefficients. These studies suggested that this should be due to the high number of genotyped individuals and registered generations in the pedigree (Ojeda-Marín et al., 2023a, 2023b). Hence, these high correlations could explain that no differences were detected in the global F_{PED} and genomic inbreeding coefficients. However, F_{PED} was the only coefficient that presented significant differences between lines with $P \leq 0.05$. This could be a combination between less effect of molecular inbreeding and more variance of the molecular inbreeding coefficients. Furthermore, we want to highlight the importance of quality control that resulted in the final sets of markers used in this study, and of the setting parameters used for determining the different genomic inbreeding coefficients. Even though there are many parameters established to define genomic inbreeding, and different protocols to make the quality control, there is still no consensus in the literature. Therefore, the studies that used genomic information to perform inbreeding depression analysis should be interpreted cautiously. However, after testing, the parameters that best fit our population were selected.

In addition, regarding the possibility of computing inbreeding in populations without pedigree information, another advantage of genomic information would be to address inbreeding coefficient of a specific region in the genome. Moreover, specific chromosomal regions could contribute disproportionately to inbreeding depression and that the identification of this regions might represent an opportunity to manage and potentially eliminate genetic variations (Curik et al., 2017). These particularities have been used to estimate ID by specific genome regions or by chromosome in different species (Saura et al., 2015; Martikainen et al., 2018; Sumreddee et al., 2019; Pilon et al., 2021; Luigi-Sierra et al., 2022; Hervás-Rivero et al., 2023). In Iberian Pigs ID was detected in chromosome 13 of the total number of piglets born and the total number of piglets born alive using the simplest proportion of homozygous sites across chromosomes and F_{ROH} per chromosome (Saura et al., 2015). Moreover, Hervás-Rivero et al. (2023) showed that there were ROH regions in chromosomes 2, 5, 7, 8 and resulting in a significant decrease in LS in two other varieties of Iberian pigs. Other authors performed a study in red deer of ID on fitness traits and detected a significant effect on the trait using F_{ROH} but no effect was detected when F_{ROH} was split into chromosomes (Hewett et al., 2024). In previous studies we detected statistically significant differences between lines in chromosomes 3, 4, 6, 8, 11, 15, and 19 (Ojeda-Marín et al., 2023b). In the present study it was detected that only F_{ROH} calculated in chromosome 13 produced significant ID in the H-Line. In the L-Line F_{ROH} resulted in a significant decrease in the LS in chromosomes 1 and 9. Furthermore, the significant differences in ID detected in most of the chromosomes between lines could be attributed to the divergent selection. Nevertheless, if ID is considered as a combined effect of the inbreeding across the genome in a trait, then each autosome F_{ROH} should be considered as a contribution to the total ID.

In humans it has been described that the longer the ROH is present the more probable it is carrying deleterious mutations (Szpiech et al., 2013). Moreover, other studies showed that in a Soay sheep population the mutation load decreases with haplotype age (Stoffel et al., 2021). However, other authors detected that short and medium ROH (> 100 kb to 3 Mb) were more loaded with deleterious variants than long ROH (> 3 Mb) in cattle populations and suggested that it might be due to selection (Zhang et al., 2015). There are many examples in the literature showing that longer segments of ROH (more recent F_{ROH}) have a lower impact on the studied traits while shorter ROH (older F_{ROH}) have no effect or a positive effect on the traits (Saura et al., 2015; Doekes et al., 2019; Makanjuola et al., 2020; Antonios et al., 2021; Tao et al., 2021). Furthermore, Sumreddee et al. (2020) showed that segment length could have different effects depending on the trait studied. These authors also showed that the segments shorter than 5 Mb could have a smaller detrimental effect on some traits, but still have a negative effect due to the accumulative effect. In our results, a greater decrease in the regression coefficient was detected when longer segments were used to calculate genomic inbreeding and a greater increase when shorter segments were used in both lines. This could be an effect of selection, with homozygosity maintaining ancient beneficial alleles related to the trait. Also, it could be an effect of the new mating system in the starting of the experiment where lower number of individuals were mated in comparison with the panmictic original population resulted in a decrease of the effective population size from 84 to approximately 30 (Formoso-Rafferty et al., 2016a; Ojeda-Marín et al., 2023a). This decrease in the effective population size could lead to a purge effect. Moreover, the H-Line presented

greater negative effects on the LS when longer segments were used than the L-Line despite the fact of being under the same mating policy. This may again emphasize the greater robustness previously observed in the L-Line. Nevertheless, other authors determined that in the presence of negative additive by dominance effects, changes in allele frequencies could be misinterpreted as purging because of the positive relationship between inbreeding and the performance (Curik et al., 2001).

In a recent study, Naji et al. (2024) showed that more recent HBD classes (15 generations) had a greater ID effect on some of the studied traits than older HBD classes in cattle. In our present results, younger classes generally resulted in a more negative effect on LS. However, the effect of the used age classes to estimate F_{HBD} was different in each selected line. In fact, splitting F_{HBD} into different ages and accumulative classes gave the most different results between lines. This approach was based on the ROH concept, but includes other factors such as allele frequencies, distance between markers or genotyping error. Therefore, this approach could increase the uncertainty in detecting HBD probabilities. Nevertheless, the general effect of the different HBD coefficients on the LS was similar in both lines: classes that were more recent produced a decrease in the trait and older classes produced a positive effect on the trait. Naji et al. (2024) showed that ID of F_{HBD} obtained from classes ≥ 64 were around 0 and did not present a significant p value. Furthermore, they concluded that the absence of effect of these older classes on the trait could be explained because there was not enough variation in these classes to have any effect. Hence, they recommended not including ancient classes from more than 50 generations ago to estimate inbreeding coefficients. Nevertheless, the SD in the classes that present a significant positive effect in our analysis was the lowest in both lines. Moreover, as mentioned above, other authors described that deleterious functional variations in the cattle genome was included in the medium to short ROH segments more than in longer segments (Zhang et al., 2015). Therefore, for this kind of population we recommend including older segments in the ID analysis.

Conclusions

In both selected lines, the relationship between F_{VR2} and the other inbreeding coefficients was the less significant while F_{PED}, $F_{YAN,}$ and F_{VR1} were more representative of the rest of coefficients. Significant negative effects of global inbreeding coefficients on the LS were detected in both lines but were lower in the H-line than in the L-Line. This difference between lines is probably related to the higher robustness of the L-Line already described. Furthermore, differences were detected in the ID of chromosomic F_{ROH} between lines: chromosomes 1, 9 and 13 were candidates of future gene search. In general, more recent F_{ROH} and F_{HBD} presented negative effects on LS and older F_{ROH} and F_{HBD} presented positive effects on LS in both selected lines. However, the effect of different length sections and age sections resulted in a different effect in each of the selected lines. These results suggested that the divergent selection for homogeneity results in different ID effect in other fitness traits as LS.

Supplementary Data

Supplementary data are available at *Journal of Animal Science* online.

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Author Contributions

Candela Ojeda-Marín (Conceptualization, Data curation, Formal analysis, Investigation, Methodology, Writing—original draft, Writing—review & editing), Isabel Cervantes (Funding acquisition, Investigation, Project administration, Supervision, Writing—review & editing), Nora Formoso-Rafferty (Resources, Writing—review & editing), Juan Pablo Gutiérrez (Investigation, Project administration, Resources, Supervision, Writing—review & editing), and S.T. Rodríguez-Ramilo (Conceptualization, Formal analysis, Investigation, Methodology, Supervision, Writing—review & editing)

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Conflict of interest statement

The authors declare no conflict of interest.

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