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Inbreeding depression and runs of homozygosity islands in Asturiana de los Valles cattle breed after 30 years of selection

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Abstract

Inbreeding depression results in a decrease in the average phenotypic values of affected traits. It has been traditionally estimated from pedigree-based inbreeding coefficients. However, with the development of single-nucleotide polymorphism arrays, novel methods were developed for calculating the inbreeding coefficient, and consequently, inbreeding depression. The aim of the study was to analyse inbreeding depression in 6 growth and 2 reproductive traits in the Asturiana de los Valles cattle breed using both genealogical and molecular information. The pedigree group comprised 225,848 records and an average equivalent number of complete generations of 2.3. The molecular data comprised genotypes of 2693 animals using the Affymetrix medium-density chip. Using the pedigree information, three different inbreeding coefficients were estimated for the genotyped animals: the full pedigree coefficient (FPED), and the recent and ancient inbreeding coefficients based on the information of the last three generations $(F_{PED < 3G})$ and until the last three generations $(F_{PED > 3G})$, respectively. Using the molecular data, seven inbreeding coefficients were calculated. Four of them were estimated based on runs of homozygosity (ROH), considering (1) the total length (F_{ROH}), (2) segments shorter than 4 megabases ($F_{ROH<4}$), (3) between 4 and 17 megabases ($F_{ROH4-17}$), and (4) longer than 17 Mb ($F_{ROH>17}$). Additionally, the three inbreeding coefficients implemented in the Plink software (F_{HAT1-3}) were estimated. Inbreeding depression was estimated using linear mixed-effects model with inbreeding coefficients used as covariates. All analysed traits (birth weight, preweaning average daily gain, weaning weight adjusted at 180 days, carcass weight, calving ease, age at first calving, calving interval) showed a statistically significant non-zero effect of inbreeding depression estimated from the pedigree group, except for the Postweaning Average Daily Gain trait. When inbreeding coefficients were based on the genomic group, statistically significant inbreeding depression was observed for two traits, Preweaning Average Daily Gain and

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Weaning Weight based on F_{ROH} , $F_{ROH>17}$, and F_{HAT3} inbreeding coefficients. Nevertheless, similar to inbreeding depression estimated based on pedigree information, estimates of inbreeding depression based on genomic information had no relevant economic impact. Despite this, from a long-term perspective, genotyped data could be included to maximize genetic progress in genetic programs following an optimal genetic contribution strategy and to consider individual inbreeding load instead global inbreeding. ROH islands were identified on chromosomes 2, 3, 8, 10, and 16. Such regions contain several candidate genes for growth development, intramuscular fat, body weight and lipid metabolism that are related to production traits selected in Asturiana de los Valles breed.

K E Y W O R D S

Asturiana de los Valles, cattle breed, inbreeding, inbreeding depression, pedigree, runs of homozygosity

1 | INTRODUCTION

The inbreeding depression is defined as the reduction in the average phenotypic value of a quantitative trait as a consequence of the increase of inbreeding caused by the mating of individuals more related than the average of the population (Crow & Kimura, 1970). There are three principal hypotheses that explain the inbreeding depression being the most plausible the 'dominance theory', although the others can also modulate it. The dominance theory argues that the favourable effects of the dominance decrease as the frequency of recessive alleles and the recessive homozygotes genotypes increase (Crow & Kimura, 1970; Lynch & Walsh, 1998). The overdominance hypothesis that assumes the superiority of the heterozygotes, and the epistatic gene interaction can also explain the inbreeding depression in populations (East, 1908; Kempthorne, 1957; Shull, 1908). However, the difficulty to include the epistatic effect in the statistical models have favoured their absence in the inbreeding depression analysis. In the absence of epistasis, a linear relationship is assumed between the inbreeding depression and the inbreeding coefficients (Crow & Kimura, 1970; Lynch & Walsh, 1998). Inbreeding depression has been classically estimated as the linear regression coefficient of the phenotype on inbreeding coefficients (defined as the probability that both alleles at any locus within the individual are identical by descent). Therefore, a major concern in inbreeding depression analysis is the methodology used to estimate inbreeding coefficients. Traditionally, pedigree records have been used to estimate inbreeding coefficients which feasibility is highly dependent of the quality of the genealogical information. Pedigree errors, genealogical depth and unbalanced information are three of the major factors affecting the bias and precision of inbreeding

depression estimated from genealogical records (Cassell et al., 2003; Curik et al., 2017; Leroy & Baumung, 2011; VanRaden, 1992). Molecular information has been an alternative to pedigree-based inbreeding coefficients estimations and the development of single nucleotide polymorphism (SNPs) arrays opened new ways to analyse inbreeding depression even in populations with incorrect or missing pedigree records. Different SNP-based inbreeding coefficients (usually called genomic inbreeding) have been postulated: (1) those referring to the homozygous SNP genotypes, (2) those derived from the diagonal of a genomic relationships matrix, and (3) those based on measures of Runs of Homozygosity (ROH) defined as contiguous regions of the genome where an individual is homozygous across all sites (Malécot, 1948; McQuillan et al., 2008; VanRaden, 2008). A recent simulation study revealed that inbreeding estimations from ROH are very precise in different scenarios (Caballero et al., 2022).

Many studies have analysed the inbreeding depression in livestock populations (Carolino & Gama, 2008; Doekes et al., 2020, 2021; Hidalgo et al., 2021; Luigi-Sierra et al., 2022; Rafter et al., 2022; Zhang et al., 2022). Traditionally it has been assumed that traits related to fitness are the ones first affected by inbreeding depression and in a higher degree than those related to morphology or physiological traits (Lynch & Walsh, 1998). However, posteriorly, analysis in domesticated breeds and wild species have questioned this assumption (Chapman et al., 2009; Leroy, 2014). Research on inbreeding in recent decades has been extensive, as revealed the meta-analysis recently published by Doekes et al. (2021) which summarized the most relevant results achieved from 154 studies, published from 1990 to 2020 on seven livestock species. The major findings revealed a (1) 0.13% decreased of a trait's mean or 0.59% of standard deviation when inbreeding depression increases by 1%, (2) fitness and non-fitness

TABLE 1 Mean, standard deviation and number of observations for the eight phenotypic traits.

| | Pedigree gr | oup | | Genomi | c group | |
|-----------------|-------------|-------|-------|--------|---------|-------|
| Trait | N | Mean | SD | N | Mean | SD |
| BW (kg) | 64,768 | 38.5 | 6.3 | 329 | 39.3 | 6.1 |
| PrWADG (kg/day) | 143,823 | 1 | 0.2 | 1458 | 1.1 | 0.3 |
| WW | 143,844 | 216.8 | 44.2 | 1458 | 245.7 | 49.4 |
| PtWADG (kg/day) | 3568 | 1.2 | 0.3 | 620 | 1.2 | 0.3 |
| CW (kg) | 215,121 | 264.6 | 67.2 | 104 | 274.8 | 62.9 |
| CE | 711,769 | 1.7 | 0.5 | 2113 | 1.5 | 0.5 |
| AFC (days) | 58,818 | 967.2 | 130.2 | 599 | 963.1 | 123.8 |
| CI (days) | 73,779 | 450.6 | 113.7 | 790 | 441.6 | 110.4 |
| | | | | | | |

Note: N: number of animals with phenotypic data; mean of the trait (Mean) and standard deviation (SD). Abbreviations: AFC, age at first calving, BW, birth weight; CE, calving ease; CI, calving interval; CW, carcass weight; PrWADG, preweaning average daily gain; PtWADG, postweaning average daily gain; WW, weaning weight.

traits are equally affected and (3) an increase in the accuracy of inbreeding depression estimation using SNP instead of pedigree information.

Asturiana de los Valles is an autochthonous cattle breed mainly located in the Cantabrian region of northern Spain. Currently, it is the Spanish autochthonous cattle breed with highest census and number of farmers, and it is located in the majority of the Spanish provinces. At present, the census is around 100,000 animals and the breeder association (ASEAVA) includes more than 3900 farmers with an average size of 26 animals per farm. Meat production is the main purpose of the breed. However, the maternal behaviour is also a desirable trait considering the semi-extensive or extensive management system of the breed. Animals show a good meat conformation, feed efficiency and a remarkable growth rate. The double muscle phenotype, associated with myostain mutation, affect muscular development of this breed resulting in higher yield carcass and muscle proportion, and lower bone and fat proportion than animals without the mutated allele (https://www.aseava.com/raza_capitulo_10.aspx). The official genetic improvement program of the breed began in 1991 and currently includes productive and morphological traits.

The objective of this study was to analyse for the first time the inbreeding depression for reproductive and nonreproductive traits using pedigree records and SNPs data after 30 years of genetic selection program in the Asturiana de los Valles bovine breed.

2 | MATERIALS AND METHODS

The data for the analysis were provided from the breeding association Asociación Nacional de la Raza Asturiana de los Valles (ASEAVA).

2.1 | Phenotypic data

The eight phenotypic traits analysed were:

- Birth Weight (BW) (kg)
- Preweaning average daily gain (PrWADG) (kg/day): computed from birth to weaning
- Weaning Weight adjusted at 180 days (WW) (kg)
- Postweaning average daily gain (PtWADG) (kg/day)
- Carcass weight (CW) (kg): adjusted by age at slaughter
- Calving ease (CE) (trait measured in the calf): Ranges from 1 to 5: Easy/Unassisted (1), Easy pull (2): Difficult calving/Hard pull (3), Caesarean (4) and abnormal presentation (5)
- Age at First Calving (AFC) (days)
- Calving interval (CI) (days) among first and second calve.

The data were analysed twice: (1) a populationwise analysis comprising the registered animals in the herdbook of the cattle breed (*pedigree group*) and (2) a genotype-wise analysis comprising 2693 genotyped (*genomic group*) animals genotyped for the medium-density Affymetrix Axiom Bovine genotyping array (v2 and v3) (Affymetrix/Thermo Fisher Scientific, Santa Clara, CA). A brief description of the phenotypic traits for both groups is given in Table 1.

2.2 | Inbreeding coefficients

2.2.1 | Pedigree group

Genealogical information was provided by the breeding association (ASEAVA). The total number of pedigree records were 225,848 that belong to animals enrolled in the

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genetic evaluation program of the breed and composed of 69,856 males and 155,992 females. The average number of equivalent complete generations of the analysed animals was 2.3 and the average generation interval of 6.5 years. The birth year of the animals ranged from 1909 to 2021. The genealogical parameters were estimated using ENDOG V4.8 software (Gutiérrez & Goyache, 2005).

2.2.2 Genomic group

The SNP genotypes of 2693 Asturiana de los Valles bovine samples were obtained from the medium-density Affymetrix Axiom Bovine genotyping array (v2 and v3) (Affymetrix/Thermo Fisher Scientific, Santa Clara, CA). The birth year of the genotyped animals ranged from 1980 to 2019 (Figure S1). The total number of SNPs was 42,537.

Pedigree records from genotyped animals was used to estimate total inbreeding (F_{PED}), recent inbreeding (inbreeding from the genealogical information of the last 3 generations, $F_{PED < 3G}$) and old inbreeding (inbreeding for the genealogical information above the last 3 generations, F_{PED>3G}) using ENDOG V4.8 software (Gutiérrez & Goyache, 2005).

ROH were detected using the Meyermans et al. (2020) criteria using the Plink 2.0 software (Purcell et al., 2007). The parameters used to detect a ROH using the sliding window method were: at least 15 homozygous SNP covering a minimum of 1 Mb with a maximum gap of 500 kb, with at least 1 SNP per 70kb, and with 1 heterozygous allowed.

F_{ROH} was estimated by:

$$F_{ROH} = \frac{l_{ROH}}{l_{aut}}$$

where l_{ROH} is the total length of all the ROH of an individual and l_{aut} is the size of the genome of Bos taurus in bp (2507.77 Mb). The ROH were grouped in three groups according to the length: <4Mb, 4-17Mb and>17Mb. Inbreeding coefficients were computed for the three measures, F_{ROH<4}, F_{ROH4-17} and F_{ROH>17}.

Three additional inbreeding coefficients implemented in plink v1.9 (Purcell et al., 2007) were computed: F_{HAT1} that is the variance-standardized relationship minus 1; F_{HAT2} that measures the excess of homozygosity; and F_{HAT3} that is the inbreeding definition of Wright estimated as the correlation between uniting gametes (Dadousis et al., 2022).

The relationships among inbreeding coefficients estimated from pedigree and molecular information were analysed using linear regression with a total least squares approach for modelling symmetric relationships.

2.3 Inbreeding depression

Inbreeding depression was estimated for each trait with linear mixed-effects models. The fixed effects included in the model were the number of calving (3 levels: first calf; second; third or later) and sex (2 levels). The inbreeding coefficients were included as covariates. The random effects taken into consideration were direct and maternal genetic effects, and the combination herd-year-season (number of levels ranging from 1121 for the genomic group to 16,642 for the pedigree group) for BW, PrWADG, WW, CW, CE, AFC and CI. The herd-year-season effect was not included for PtWADG because this trait is measured in homogeneous conditions in a testing station.

In matrix notation, the model can be written as follows:

$$y = Xb + Za + Wm + Vq + e$$

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| е | | 0 | | 000R | J |

where $\mathbf{G} = \mathbf{A}\sigma_a^2$, $\mathbf{M} = \mathbf{A}\sigma_m^2$, $\mathbf{C} = \mathbf{A}\sigma_{am}$, $\mathbf{Q} = \mathbf{I}_q \sigma_q^2$, and $\mathbf{R} = \mathbf{I}_{\mathbf{n}} \sigma_{e}^{2}$; y is the vector of trait observations; b is a vector of non-genetic effects, that include the inbreeding coefficient effect; *a* is the vector of the random additive genetic effects; *m* is a vector of the random maternal additive genetic effects; q is a vector of random herd-year-season effects, and e is the vector of residuals. X, Z, W, and V are incidence matrices relating **a**, **m**, and **q** to **y**. **A** is the pedigree-based additive numerator relationship matrix. σ_a^2 is the variance of direct additive genetic effects, σ_m^2 is the variance of maternal additive genetic effects, σ_{am} is the covariance between direct and maternal additive genetic effects, σ_a^2 is the variance of permanent environmental effect, and σ_e^2 is the residual variance. $\mathbf{I}_{\mathbf{q}}$ and $\mathbf{I}_{\mathbf{n}}$ are identity matrices with order respectively equal to q, the number of environments, and *n* is the number of observations.

Programs RenumF90 and BlupF90+ of the BLUPF90 family were used for the analyses (Misztal et al., 2002).

Selection signatures 2.4

ROH pattern analysis has been used to evidence highly inbred genomic regions, called ROH islands (Nothnagel et al., 2010). ROH islands are signals of positive selection due to linkage disequilibrium and have been largely analysed in livestock species (Gorssen et al., 2021; Peripolli et al., 2018). Following the procedure of Biscarini et al. (2020) ROH incidence (%SNP in ROH) was identified counting the number of times that a SNP is included in a ROH and dividing such value by the total number of animals. Finally, ROH islands are those where SNPs included in a ROH had a higher value than a specific threshold defined as 99.9 percentile. Therefore, SNPs from the top 0.1% are selected as indicative of ROH islands. The identification of the genes located in the ROH islands within the highly homozygous genomic regions detected was obtained from the Ensembl Genome Browser tool (https:// www.ensembl.org/index.html) that uses the *Bos taurus* genome assembly ARS-UCD1.2 as reference. The Cattle Quantitative Trait Loci (QTL) Database (Animal QTLdb) (https://www.animalgenome.org/cgi-bin/QTLdb/BT/ index) was used to find possible QTL previously defined in the ROH islands identified.

3 | RESULTS AND DISCUSSION

3.1 | Inbreeding coefficients

Summary statistics of different inbreeding coefficients estimated from pedigree and SNP's of the genomic group are shown in Table 2. The major concerns of the inbreeding coefficients estimated from pedigree records are related to the quality and depth of the genealogical information. The average number of equivalent complete generations of the Asturiana de los Valles breed is 2.3, therefore, on average, only the two parents, 4 grandparents and a third of the great-grandparents of the individuals are known. This value is in the lower range of the values achieved in other Iberian Peninsula cattle breeds that range from 1 in Bruna dels Pirineus to 4.6 in Pirenaica (García-Atance et al., 2023). Previous studies achieved inbreeding coefficients using genealogical records from the whole population of the Asturiana de los Valles breed around 1%, so such value may be probably underestimated due to the lack of completeness of the pedigree (Gutierrez 4390388, 0, Downloaded from https://onlinelibrary.wiley.com/doi/10.11111/jbg.12853 by Spanish Cochrane

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et al., 2003). The F_{PED} and $F_{PED<3G}$ shown similar values with a skewed left-peak shape and an average value of 1.3% and 1% respectively. The $F_{PED>3G}$ value (0.3%) evidenced the limited depth of the Asturiana de los Valles breed pedigree records.

The identification of ROH is affected by the SNP density of the chip used, the final number of SNPs after the filtering procedure and the parameters used to identify them. In this study, the rules suggested by Meyermans et al. (2020) for an adequate and robust ROH analysis in PLINK on medium-density SNP data were used. FROH average was 7.6%, and as the fragment length used increased, the inbreeding coefficient decreased from 6.1% in $F_{ROH<4}$ to 0.5% in F_{ROH>17}. All the ROH inbreeding coefficients showed a peak-shaped distribution skewed to the right being less evident for F_{ROH<4} values. F_{ROH} is highly dependent of the density of the SNPs and the parameters used in their identification, therefore, comparison among studies must be done with caution. However, our F_{ROH} agreed with those obtained in other cattle breeds using similar parameters to identify the ROH (Meyermans et al., 2021) and also similar to other Spanish and Italian cattle breeds or in the upper range than a set of 96 European bovine breeds analysed using different parameters for ROH identification (Mastrangelo et al., 2020).

 F_{HAT1} and F_{HAT2} showed negative average values, -9.8 and -0.1 respectively and the higher ranges (5.9 and 6.1). F_{HAT3} achieved an average value close to 0, similar than F_{HAT2} but with opposite sign and higher range (from -0.17 to 0.27).

3.2 | Correlations among the inbreeding coefficients

The correlations among the different inbreeding coefficient estimators are shown in Table 3. F_{PED} and

| TABLE 2 | Summary statistics of the inbreeding coefficients (%) estimated from the two different sources of information, pedigree (F_{PED}) |
|--------------------------|---|
| and SNPs (F _R | $_{\rm ROH}$ and $\rm F_{\rm HAT}$). |

| | Average | SD | Median | Kurtosis | Asymmetry | Minimum | Maximum |
|------------------------|---------|------|--------|----------|-----------|---------|---------|
| F _{PED} | 1.3 | 0.04 | 0 | 23.3 | 4.7 | 0 | 0.32 |
| F _{PED<3G} | 1.0 | 0.04 | 0 | 24.9 | 4.9 | 0 | 0.31 |
| $F_{PED>3G}$ | 0.3 | 0.01 | 0 | 44.1 | 5.3 | 0 | 0.12 |
| F _{ROH} | 7.6 | 0.03 | 0.07 | 26.1 | 4.5 | 0.03 | 0.37 |
| F _{ROH<4} | 6.1 | 0.01 | 0.06 | 7.8 | 0.7 | 0.03 | 0.13 |
| F _{ROH 4-17} | 0.9 | 0.01 | 0.01 | 19.8 | 3.8 | 0 | 0.13 |
| F _{ROH>17} | 0.5 | 0.02 | 0 | 48.0 | 6.2 | 0 | 0.27 |
| F _{HAT1} | -9.8 | 0.22 | -0.13 | 219.7 | 12.7 | -0.33 | 5.5 |
| F _{HAT2} | -0.1 | 0.23 | 0.04 | 211.9 | -12.5 | -5.7 | 0.34 |
| F _{HAT3} | 0.1 | 0.03 | -0.003 | 19.5 | 3.2 | -0.17 | 0.27 |

F_{PED<3G} were strongly correlated and both showed weaker correlations with $F_{PED>3G}$. F_{PED} and $F_{PED<3G}$ correlations with ROH estimators ranged from 0.37 to 0.42 except for $F_{ROH < 4Mb}$ (ancestral inbreeding) that was 0. On the contrary, F_{PED>3G} correlations with ROH estimators were much lower, probably as a consequence of the limited depth of the pedigree records. The correlations among F_{PED} and F_{HAT1-3} was not statistically significant different from 0 or close to 0 except for F_{HAT3} - F_{PED} and F_{HAT3} - $F_{PED>3G}$ that achieved correlation values around 0.4. Previous studies have achieved intermediate values for correlations between inbreeding coefficients estimated from pedigree and SNPs, ranging from 0.4 to 0.8, but even negative values or close to 0 have been previously reported (Caballero et al., 2022). Our results are located in the lower values of the range, probably due to the limited depth of the pedigree records. It is well known that the more the pedigree quality and depth increase, the more the correlations among the different inbreeding coefficients increase (Caballero et al., 2022). This is more evident in the correlations among F_{ROH<4}, ancestral inbreeding, and pedigree inbreeding coefficients that are close to 0.

The ROH-based estimators achieved the higher correlation values among FROH, FROH4-17 and FROH>17 ranging 0.68-0.91. F_{ROH<4} inbreeding coefficients, evidenced the lowest correlation values being negative with F_{ROH>17}. The same tendency was shown among inbreeding coefficients estimated from ROH and F_{HAT1-3}; except for F_{ROH<4}, the correlations coefficients ranged from 0.79 to 0.89 with F_{HAT3} being lower among all ROH inbreeding coefficients and F_{HAT1-2}. F_{HAT1} and F_{HAT2} showed a strong negative correlation (-0.97) and F_{HAT3} achieved not significantly greater than 0 or weak correlation with F_{HAT2} and F_{HAT3} , respectively.

3.3 **Inbreeding depression**

Estimates of the inbreeding depression for the traits analysed are shown in Table 4. Statistically significant inbreeding depression was observed for all traits analysed for the pedigree group, except PtWADG. However, the reduction in the mean phenotypic value, estimated as the ratio between the inbreeding depression value and the phenotypic average, was very limited, ranging from 0.03% in calving ease (0.05/1.7) to 0.21% in carcass weight (55.5/264.6) by each 1% of increase in inbreeding. Consequently, the reduction of the average phenotypic values of the traits as a consequence of the inbreeding depression would not have a notable economic impact, for example a 1% of inbreeding increase would decrease in of 0.555 kg the average carcass weight (264.6 kg).

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When inbreeding was based on genomic estimates, statistically significant inbreeding depression was observed only for PrWADG and WW and both for the same inbreeding coefficient estimators, i.e., F_{HAT3}, F_{ROH} and $F_{ROH>17}$. Vogelzang (2018) evidenced that a subset of animals (n=1000) are enough to detect and characterize ROH and obtain similar results to that found in the entire population. Only three traits showed more than that value and two of them evidenced statically significant inbreeding depression, so the number of observations of the traits in the genomic group could have underestimated the inbreeding depression effect. In addition, no inbreeding depression was observed for ancient or medium inbreeding coefficients ($F_{ROH<4}$ and $F_{ROH4-17}$). Probably, the purging effect in old generations of deleterious alleles could explain such result (Mc Parland et al., 2009). Asturiana de los Valles cattle breed, as other local cattle breeds, has relative small census and in such conditions, purging is effective in reducing the inbreeding load. Significant values of inbreeding depression were at least twice as low when using pedigree records as when using genomic data. This fact could be explained because the total least square regression model indicates that the best fit occurs with a slope about two for the regression of F_{PED} on F_{ROH} (Figure S2). That means that a change of one unit in F_{ROH} represents a change of two units in F_{PED}, then, when a third variable (inbreeding depression) is regressed on F_{ROH}, its regression coefficient tends to be larger than when regressed on F_{PED}. However, similar to inbreeding depression estimated based on pedigree information, estimates of inbreeding depression based on genomic information had no relevant economic impact. Indeed, the reduction of phenotypic values in the traits that have shown significant inbreeding depression ranged for 0.75 to 1.7 kg for WW and 0.004 to 0.01 g/day for PrWADG by each 1% of increase of inbreeding. One of the main concerns in estimating inbreeding depression is the type of information used to calculate the inbreeding coefficient. Since the development of large-scale SNP arrays in livestock species, genomic information has been used extensively to estimate inbreeding coefficients and has replaced or complemented pedigree records in such studies. A recent study achieved that among 11 different inbreeding coefficients measures based on pedigree and genomic information, F_{HAT3} provides the most accurate inbreeding depression estimation, F_{ROH} is very precise in all the scenarios simulated in the study and genomic estimates of inbreeding depression are more accurate than those based on genealogical information (Caballero et al., 2022). The completeness of Asturiana de los Valles genealogical records is relatively low (average number of equivalent complete generation is 2.3); therefore, pedigree records would not be the optimal to

F_{ROH<4}

F_{ROH 4-17}

F_{ROH>17}

F_{HAT1}

F_{HAT2} *p < 0.05. nimal Breeding and Genetics

0.14*

0.79*

0.81*

-0.02

0.27*

| | | | | in pair of more | eaning econnected | | peargree in | | |
|------------------------|------------------------|------------------------|------------------|-----------------------|-----------------------|------------------------|-------------------|-------------------|-------------------|
| genotypes. | | | | | | | | | |
| | F _{PED<3G} | F _{PED>3G} | F _{ROH} | F _{ROH<4} | F _{ROH 4-17} | F _{ROH>17} | F _{HAT1} | F _{HAT2} | F _{HAT3} |
| F _{PED} | 0.98* | 0.30* | 0.42* | 0.01 | 0.39* | 0.38* | 0.01 | 0.09* | 0.38* |
| F _{PED<3G} | | 0.12* | 0.4* | 0 | 0.37* | 0.38* | 0.01 | 0.08* | 0.37* |
| F _{PED>3G} | | | 0.17* | 0.05 | 0.19* | 0.12* | -0.02 | 0.05* | 0.13* |
| F _{ROH} | | | | 0.16* | 0.88* | 0.91* | 0.02 | 0.21* | 0.89* |

0.05

TABLE 3 Pairwise Pearson correlations between each pair of inbreeding coefficient estimators from pedigree information and SNP

estimate inbreeding depression if molecular data are available. The high amount of available information for pedigree records probably explains that all the traits, except PtWADG, showed a significant inbreeding depression effect for the genealogical analysis. But, when the analysis from pedigree records only includes animals with genomic data, the phenotypic data do not evidenced inbreeding depression even though the pedigree records of the genotyped animals are deeper (average number of equivalent complete generations 3.9). It has been noticed that partial pedigrees reduce the average inbreeding estimate and the variance of such estimates. As a consequence, inbreeding depression estimations obtained from incomplete pedigrees will not necessarily produce the same than from complete ones (Cassell et al., 2003). Such results may indicate that probably estimates of inbreeding and inbreeding depression should be more reliably obtained from molecular markers than from pedigrees, as other authors have shown previously (Caballero et al., 2022; Wang, 2016).

Despite it is not expected a noticeable economic impact for the breeders as a consequence of the inbreeding depression in the short term, it should be considered a long-term evaluation of the inbreeding depression economic impact to minimize it. Inbreeding control in Asturiana de los Valles breed is based in breeding plans avoiding mating between relatives according to pedigree records. However, inbreeding coefficients based on ROH provide more accurate estimations of inbreeding coefficients and inbreeding depression than pedigree records. Consequently, genotyped data could be incorporated in current breeding programs to maximize genetic progress controlling the short- and long-term effects in an optimal genetic contribution strategy (Meuwissen, 1997). In addition, it would be interesting to take into account individual inbreeding loads instead global inbreeding. Such procedure, could be used to select among the individuals

with high genetic values those which lower inbreeding loads to control inbreeding depression in the future generations (Casellas, 2018; Varona et al., 2019).

-0.15

0.03

0.06*

0.18*

0.17*

0.15* -0.97*

4 **ROH ISLANDS**

 -0.14^{*}

0.68*

The average length of the ROH was 6.7 Mb and ranged from 12.7 Mb (BTA1) to 3 Mb (BTA25) (Figure 1a). The total number of ROH was 270,146 and their chromosomal distribution evidenced a general trend with a higher number of ROH as the chromosome length increase (Figure 1b). The total number of ROH varied from 3148 (BTA25) to 18,315 (BTA1) with an average per chromosome of 9298.

ROH approaches have become a standard tool for selection signatures identification in cattle since the first article published in 2010 (Gorssen et al., 2021). In total, five ROH islands (ROH_I) were identified in chromosomes BTA2, BTA3, BTA8, BTA10 and BTA16 (Figure 2) with an average length of 644.3 Kb ranging from 92,273 to 920,574 base pairs. The average number of times that a SNP was detected in a ROH divided by the total number of animals with this SNP included in the ROH islands was 44, ranging from 40.1 to 47.2.

ROH, identified in our study overlapped QTL identified in cattle. For example, ROH_I-BTA2 and ROH_I-BTA3 overlapped QTL related to postnatal growth and ROH_T-BTA8 overlapped QTL related to meat texture (Davis et al., 2008; Peters et al., 2012; Rolf et al., 2012).

The total number of genes included in ROH_I were 32 (14 in BTA2; 1 BTA3; 13 BTA8; 2 BTA10 and 2 BTA16) (Table S1). Several genes located in the ROH_I identified have been previously associated with traits of interest in cattle breeds.

ROH_I-BTA2 contain three candidate genes (*HCRTR1*, FABP3, and SDC3) related to cattle traits of interest as

| | | BW (kg) | | | PrWADG | (kg/day) | | WW (kg) | | | PtWAD | G (kg/day | (|
|---------------|---------------------------------|---------|-------|---------|-------------|----------|---------|--------------|-------|---------|-----------|-----------|--------|
| | | ID | SE | Ν | Ð | SE | Ν | D | SE | Ν | D | SE | N |
| Genomic Group | F_{PED} | 9.8 | 6.7 | 327 | -0.2 | 0.1 | 1453 | -34.5 | 24.2 | 1453 | -0.38 | 0.4 | 613 |
| | $\mathrm{F}_{\mathrm{PED<3G}}$ | 11.2 | 7,0 | 327 | -0.22 | 0.1 | 1453 | -37.8 | 25.1 | 1453 | -0.21 | 0.4 | 613 |
| | $F_{PED>3G}$ | -11 | 33.8 | 327 | 0.14 | 0.7 | 1453 | 16.7 | 128.8 | 1453 | -1.94 | 1.2 | 613 |
| | $\mathrm{F}_{\mathrm{ROH}}$ | 6.6 | 10.4 | 329 | -0.57* | 0.2 | 1459 | -104.3^{*} | 37.8 | 1459 | -0.35 | 0.4 | 621 |
| | $\mathrm{F}_{\mathrm{ROH}<4}$ | 16.5 | 45.6 | 329 | -0.9 | 0.9 | 1459 | -169.5 | 161.5 | 1459 | 0.96 | 1.7 | 621 |
| | $\mathrm{F}_{\mathrm{ROH}4-17}$ | 9.4 | 23.8 | 329 | -0.75 | 0.5 | 1458 | -138.8 | 83,0 | 1458 | -0.76 | 0.9 | 620 |
| | $\mathrm{F}_{\mathrm{ROH}>17}$ | 11 | 17.4 | 327 | -0.95* | 0.3 | 1453 | -171.2* | 61,0 | 1453 | -0.67 | 0.7 | 613 |
| | $\mathrm{F}_{\mathrm{HAT1}}$ | 0.2 | 1.2 | 329 | -0.02 | 0,0 | 1459 | -3.3 | 4.3 | 1459 | 0.03 | 0,0 | 621 |
| | $\mathrm{F}_{\mathrm{HAT2}}$ | -0.2 | 1.1 | 329 | 0.01 | 0,0 | 1459 | 0.9 | 4.1 | 1459 | -0.04 | 0,0 | 621 |
| | $\mathrm{F}_{\mathrm{HAT3}}$ | 0.6 | 9.7 | 329 | -0.41^{*} | 0.2 | 1459 | -75.3* | 34.2 | 1459 | -0.79* | 0.4 | 621 |
| PG | Pedigree | -4.1* | 0.6 | 64,768 | -0.14^{*} | 0.01 | 143,823 | -35.4* | 2.4 | 143,844 | -0.09 | 0.14 | 3568 |
| | | CW (kg) | | | CE | | | AFC (days) | | | CI (days) | | |
| | | ID | SE | Ν | ID | SE | Ν | ID | SE | Ν | D | SE | N |
| Genomic Group | F_{PED} | 44.4 | 62.3 | 104 | 0.1 | 0.2 | 2102 | -52.3 | 135 | 598 | 92.5 | 106.5 | 789 |
| | $F_{PED<3G}$ | 50.4 | 65.4 | 104 | 0.2 | 0.2 | 2102 | -63.9 | 141 | 598 | 104.1 | 109.9 | 789 |
| | $F_{PED>3G}$ | -83.2 | 485.6 | 104 | -2.6 | 1.3 | 2102 | 154.6 | 679 | 598 | -157.4 | 588.1 | 789 |
| | $\mathrm{F}_{\mathrm{ROH}}$ | -124.1 | 100.6 | 104 | 0.02 | 0.4 | 2114 | -100.4 | 225 | 599 | 39.9 | 159.2 | 790 |
| | $\mathrm{F}_{\mathrm{ROH}<4}$ | 15.9 | 576.4 | 104 | 2.9 | 1.6 | 2114 | 366.3 | 794 | 599 | 636.8 | 640.8 | 790 |
| | ${ m F}_{ m ROH~4-17}$ | -215.8 | 275.0 | 104 | -0.17 | 0.8 | 2112 | -1043.1 | 533 | 599 | -305.9 | 358.4 | 790 |
| | F _{ROH>17} | -199.7 | 145.3 | 104 | -0.25 | 0.6 | 2103 | 148.6 | 358 | 598 | 157.5 | 255.1 | 789 |
| | $\mathrm{F}_{\mathrm{HAT1}}$ | -27.3 | 48.4 | 104 | 0.01 | 0,0 | 2114 | -6.9 | 26 | 599 | -9,0 | 19,0 | 790 |
| | $F_{\rm HAT2}$ | -24.1 | 48.1 | 104 | -0.02 | 0,0 | 2114 | -0.2 | 23 | 599 | 10.3 | 17.7 | 790 |
| | $F_{\rm HAT3}$ | -89.8 | 90.1 | 104 | -0.32 | 0.3 | 2114 | -209.7 | 197 | 599 | 81.4 | 141.8 | 790 |
| PG | Pedigree | -55.5* | 2.12 | 215,121 | 0.05* | 0 | 711,769 | 38,7* | 13,5 | 58,818 | 42,3* | 11,9 | 73,779 |

average daily gain; WW, weaning weight adjusted at 180 days. $^{*}p < 0.05.$

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FIGURE 1 ROH length per chromosome in Mb. The black dots show the average value in Mb (a). Number of ROH per chromosome (×1000). The bold horizontal line represents the number of ROH per chromosome global average (9298) (b).





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feeding behaviour, intramuscular fat and body weight. The Hypocretin Receptor 1 (HCRTR1) belongs to the superfamily of G-coupled receptors and is involved in feeding and drinking behaviours (Fukunaka et al., 2007). Also, it has been associated with the superior ability of some African cattle breeds to maintain body weight and resist listlessness and emaciation following trypanosome infection (Kim et al., 2017; Kunii et al., 1999; Steverding, 2008). Fatty Acid Binding Protein 3 (FABP3) has been associated with intramuscular fat content in domestic animals and as a consequence to the sensory quality traits of meat production (Mateescu et al., 2015). In addition, it has been documented a different expression profile among high or low marbled beef (Lim et al., 2015). The gene Syndecan 3 (SDC3) has been previously associated with feeding behaviour and body weight (Li et al., 2023). Also, a recent study found a statistically significant association among SDC3 gene and body height, body length, chest circumference, and circumference of cannon bone in cattle (Yong-Zhen et al., 2016).

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ROHI-BTA8 overlapped one previously described candidate genes: Insulin-Like Growth Factor Protein 1 (IGF-1) influencing milk traits in cattle. *IGFBP* are a family of proteins whose function are closely related to *insulin-like growth factor proteins* (*IGF*) that has been shown to be associated with fertility, growth, and development in cattle and also with dairy traits as milk, fat and protein yield (Mullen et al., 2011). It is well known that *IGF-1* is an intermediated of the growth hormone responses in the body, acting in most cells of different tissues but especially in muscle and bones (Khounsaknalath et al., 2021).

The ROH_I-BTA10 overlapped three candidate genes related to low fertility in Holstein bulls (Nani & Peñagaricano, 2020); *ARID4 (AT-rich Interactive Domain-Containing Protein 4A)* that regulates Sertoli cells in spermatogenesis, *TOMM20L (Translocase of Outer Mitochondrial Membrane 20-Like)* that has relevant influence in important sperm functions such as motility and viability and *DAAM1 (Disheveled-Associated Activator of Morphogenesis 1)* with a crucial role in cytoskeletal organization in testis and sperm production in rats (Nani & Peñagaricano, 2020).

ROH_I-BTA16 harboured three genes (*ANGPTL7*, *MASP2*, *and EXOSC10*) related to lipid metabolism, role against infections and longevity. *Angiopoietin-Like 7* (*ANGPTL7*) is involved in the lipid metabolism and the regulation of triglyceride and cholesterol levels, as well as the production of fatty acids and the regulation of glucose metabolism and insulin sensitivity. Also, it is involved in the endochondral bone formation, obesity and fasting blood triglyceride plasma and as a consequence, it has been considered as a candidate gene in meat production animals (Abu-Farha et al., 2017; Almasi et al., 2020;

Johannessen et al., 2007). The gene *MBL-Associated Serine Protease 2* (*MASP2*) as the central protease of complemental system plays an important role in the defensive against infections (Beltrame et al., 2015). As a consequence, it has been associated with multiple human diseases but also has shown significant relationships with mastitis and milk quality in cattle breeds (Haiyan et al., 2019). Finally, *MASP2* and *Exosome Component 10* (*EXOSC10*) have also been associated with longevity in Holstein cattle (Liu et al., 2021).

Asturiana de los Valles breed has been under selection over the last 30 years. Weaned calf is the major commercial product of the breed and it has been highlighted their meat health properties due to the high ratio of polyunsaturated/saturated fatty acids (Sevane et al., 2014). Genes related to body weight, intramuscular fat, growth development and lipid metabolism were found in the ROH islands identified; therefore, it is plausible that these genes may be under positive selection. In addition, the semi-extensive traditional management of the breed could explain the signal found in chromosome regions that contain genes that play an important role against infections or milk production. It is remarkable that animals can be in extensive conditions without stabling up to 5-6 months per year and the rusticity and maternal behaviour are highly desirable characteristics. However, further studies using higher density array data or complete gene sequences would be particularly relevant to validate these candidate genes.

5 | CONCLUSIONS

We observed inbreeding depression in several traits related to growth and reproductive traits in Asturiana de los Valles cattle. In particular, increased pedigree-based inbreeding coefficient was associated with inbreeding depression in all traits analysed except one, while genomic inbreeding estimates were associated with impaired phenotypic performance in 180-days adjusted weaning weight and preweaning- and postweaning average daily gain. In addition, we discovered selection signatures in the genome of Asturiana de los Valles breed. A total of five ROH islands, in chromosomes (BTA2, BTA3, BTA6, BTA8 and BTA16) that contain several QTL and candidate genes associated with feeding behaviour, body weight, growth development, intramuscular fat and lipid metabolism in cattle were discovered in our study. An optimal genetic contribution strategy or individual inbreeding load could be incorporated in breeding programs to evaluate the long-term impact of inbreeding depression on the selected traits in Asturiana de los Valles cattle. Finally, further studies using higher density array data or complete gene sequences would be essential to evaluate the effect of

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the candidate genes within the selected genomic regions discovered in this study.

AUTHOR CONTRIBUTIONS

Conceptualization: Oscar Cortes, Javier Cañon and Carlos Carleos. Analysis: Carlos Carleos and Javier Cañon. Oscar Cortes wrote the first draft of the manuscript. Carlos Carleos, Javier Cañon, Sara Andrino and María Fernanadez review and editing the article. All authors contributed to the interpretations of the results, the discussion and prepared the final manuscript. All authors read and approved the final manuscript.

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CONFLICT OF INTEREST STATEMENT

The authors declare that they have no competing interests.

DATA AVAILABILITY STATEMENT

The datasets generated and/or analysed during the current study are available from the corresponding author upon reasonable request.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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