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ORIGINAL ARTICLE

Genomic predictions and GWAS for heat tolerance in pigs based on reaction norm models with performance records and data from public weather stations considering alternative temperature thresholds

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Abstract

Genetic improvement of livestock productivity has resulted in greater production of metabolic heat and potentially greater susceptibility to heat stress. Various studies have demonstrated that there is genetic variability for heat tolerance and genetic selection for more heat tolerant individuals is possible. The rate of genetic progress tends to be greater when genomic information is incorporated into the analyses as more accurate breeding values can be obtained for young individuals. Therefore, this study aimed (1) to evaluate the predictive ability of genomic breeding values for heat tolerance based on routinely recorded traits, and (2) to investigate the genetic background of heat tolerance based on single-step genome-wide association studies for economically important traits related to body composition, growth and reproduction in Large White pigs. Pedigree information was available for 265,943 animals and genotypes for 8686 animals. The studied traits included ultrasound backfat thickness (BFT), ultrasound muscle depth (MDP), piglet weaning weight (WW), off-test weight (OTW), interval between farrowing (IBF), total number of piglets born (TNB), number of piglets born alive (NBA), number of piglets born dead (NBD), number of piglets weaned (WN) and weaning-to-estrus interval (IWE). The number of phenotypic records ranged from 6059 (WN) to 172,984 (TNB). Single-step genomic reaction norm predictions were used to calculate the genomic estimated breeding values for each individual. Predictions of breeding values for the validation population individuals were compared between datasets containing phenotypic records measured in the whole range of temperatures (WR) and datasets containing only phenotypic records measured when the weather station temperature was above 10°C (10C) or 15°C (15C), to evaluate the usefulness of these datasets that may better reflect the within-barn temperature. The use of homogeneous or heterogeneous residual variance was found to be trait-dependent, where homogeneous variance presented the best fit

for MDP, BFT, OTW, TNB, NBA, WN and IBF, while the other traits (WW and IWE) had better fit with heterogeneous variance. The average prediction accuracy, dispersion and bias values considering all traits for WR were 0.36 ± 0.05, −0.07 ± 0.13 and 0.76 ± 0.10, respectively; for 10C were 0.39 ± 0.02, −0.05 ± 0.07 and 0.81 ± 0.05, respectively; and for 15C were 0.32 ± 0.05, −0.05 ± 0.11 and 0.84 ± 0.10, respectively. Based on the studied traits, using phenotypic records collected when the outside temperature (from public weather stations) was above 10°C provided better predictions for most of the traits. Forty-three and 62 candidate genomic regions were associated with the intercept (overall performance level) and slope term (specific biological mechanisms related to environmental sensitivity), respectively. Our results contribute to improve genomic predictions using existing datasets and better understand the genetic background of heat tolerance in pigs. Furthermore, the genomic regions and candidate genes identified will contribute to future genomic studies and breeding applications.

KEYWORDS

climatic resilience, heat stress, maternal-line pigs, weather station data

1 | INTRODUCTION

Climate change has negatively impacted livestock production (Bernabucci, 2019; Vilas Boas Ribeiro et al., 2018), indicating that there is a need to develop effective strategies for mitigating the effects of heat stress (HS). Genetically improving animals is an effective and long-lasting alternative to improve the productive efficiency and adaptation of animals to certain environments. However, increased productivity has led to greater metabolic heat production (Cabezón et al., 2016; Stinn & Xin, 2014). In the swine industry, HS is considered one of the major welfare and productive issue as global temperatures rise. HS is directly associated with poor growth performance, lower carcass quality, decreased feed efficiency and fertility issues (Baumgard & Rhoads Jr., 2013; Johnson, 2018; Mayorga et al., 2018; Renaudeau et al., 2012).

Several studies have investigated the genetic background of HS response in swine and defined the best critical periods and climatic variables to be used when predicting animal performance in adverse climatic conditions (Carabaño et al., 2017; Chen et al., 2021; Freitas et al., 2021; Misztal, 2017; Shi et al., 2021; Tiezzi et al., 2020; Zhang et al., 2019). These studies have shown that there is genetic variability for heat tolerance and that genetic progress can be achieved through direct genetic and genomic selection for improved climatic adaptation. Genetic studies have used public weather station data to study HS in swine and have shown that accurate results can be achieved when selecting for improved heat tolerance. However, the outside climatic measurements (from public weather stations) may not reflect the actual in-barn conditions due to mitigation strategies that producers implement, such as heaters, evaporative pads, elevated airspeed and floor heating or cooling (Mayorga et al., 2019). Therefore, in the absence of within-barn climatic data, the use of only phenotypic data that were collected when the outside temperature was above a threshold should be evaluated.

The single-step Genomic Best Linear Unbiased Prediction method (ssGBLUP) is a method that simultaneously combines data from genotyped and non-genotyped individuals when performing genomic prediction of breeding values (Misztal et al., 2009; Piccoli et al., 2018). This approach combined with random-regression-based reaction norm models (RNM) allows the use of information from individuals even if they were recorded in just one environment (Hayes et al., 2016), since the response of each individual to environmental variation is modelled through a unique random regression curve that has its trajectory determined by the environmental gradient. In addition, the use of pedigree and genomic information in the ssGBLUP approach reflects the current reality of most livestock breeding programs, where not all individuals are genotyped, while providing similar or better results than other methods (Cesarani et al., 2021; Guarini et al., 2018; Mancisidor et al., 2021). In this context, the overall goal of this study was to evaluate the use of different threshold temperatures and their impact on the model predictive ability of genomic breeding values. Thus, the main objectives of this study were (1) to evaluate the accuracy, bias, dispersion and individual theoretical accuracies for

heat tolerance based on body composition, growth and reproductive traits by fitting reaction norm models through ssGBLUP, (2) to assess the impact of excluding phenotypic data based on different temperature thresholds in the prediction metrics (validation accuracy, bias and dispersion) and (3) to investigate the genetic background of heat tolerance by identifying candidate genes and biological pathways that are associated with HS response in Large White pigs for various body composition, growth and reproductive traits.

2 | MATERIALS AND METHODS

Animal welfare and ethics committee approval was not needed for this study as all the datasets used were provided by commercial breeding operations.

2.1 | Phenotypic, genotypic and pedigree data

The pedigree, phenotypic and genomic datasets were provided by the Smithfield Premium Genetics company (Rose Hill, North Carolina, USA). Phenotypic nucleus-herd records were obtained from January 2004 to December 2019, distributed among 33 farms located in North America, as described by Freitas et al. (2021). The traits analysed were: ultrasound backfat thickness (BFT; mm), ultrasound muscle depth (MDP; mm), off-test weight (OTW; kg), interval between farrowings (IBF; days), total number of piglets born (TNB), number of piglets born alive (NBA), number of piglets born dead (NBD), number of piglets weaned (WN), weaning weight of the piglets (WW; kg) and weaning to estrus interval (IWE; days). BFT, MDP and OTW were measured at around 5.5 months of age. Contemporary group was defined by the concatenation of farrowing year, farrowing season and farrowing farm for the reproductive traits, and of birth year, birth season and birth farm for the growth and body composition traits, respectively. The phenotypic datasets were edited independently for each trait by removing records deviating 3.5 SD from the mean.

A total of 8992 animals (Large White breed) were genotyped using different marker panels. The PorcineSNP10K, PorcineSNP50, PorcineSNP60K and PorcineSNP80K SNP chip panels (Illumina, San Diego, CA, USA) containing 8652, 50,549, 57,019 and 64,577 SNPs, respectively, were used for genotyping 886, 5706, 865 and 1535 animals, respectively. In the end, 8686 animals with call rate greater than 0.90 were kept for further analyses. Genotype imputation was performed as described by Chen et al. (2021). In summary, the genotypes were imputed in the following sequence: from the 10 K to the 50 K panel and then from the 50 K or 60 K to the 80 K panel. Quality control (QC) of the genotype dataset consisted of removing SNPs with a call rate below than 0.90, minor allele frequency lower than 0.01, the difference between observed and expected heterozygous frequencies lower than 0.15, and SNPs located on non-autosomal chromosomes. These filtering criteria were applied using the BLUPF90 family programs (Masuda, 2018; Misztal et al., 2018). In the end, 53,031 informative SNPs located on 18 autosomes for 8686 animals were included in subsequent analyses. The pedigree information comprised 265,943 animals, representing up to 18 generations.

2.2 | Environmental variables

Public weather station records for all farms were obtained from the Local Climatological Data at the National Oceanic and Atmosphere Administration, NOAA (www.ncdc.noaa.gov/cdo-web/datatools/lcd?prior%2520=%2520N) as described by Freitas et al. (2021). The average distance between the public weather station and the farms was 30 km (ranging from 7 to 64 km). Based on a previous study utilizing the same datasets (Freitas et al., 2021), only relative humidity (RH) and average maximum temperature (MaxT) were considered as the environmental gradient for the genomic analyses. In this study, the used environmental variable (ENV) for BFT, MDP, NBD, WN and WW was RH and MaxT was used for OTW, TNB, NBA, IBF and IWE.

2.3 | Statistical analyses

The best statistical model to describe each trait was defined in Freitas et al. (2021) and is shown in Table 1. The genetic analyses were performed following the ssGBLUP approach (Aguilar et al., 2010; Christensen & Lund, 2010; Misztal et al., 2009) considering homogenous (RNM1) or heterogeneous (RNM2) residual variances. The general model can be described as:

$$y_i = \alpha + \mathbf{x}_i'\boldsymbol{\beta} + \omega\hat{\varphi}_k + \Sigma_i\left(n_{0i} + n_{1i}\hat{\varphi}_k\right) + e_i,$$

where y_i is the phenotype observation of animal i; α is the intercept; $\mathbf{x}_i'$ is the row incidence vector for $\boldsymbol{\beta}$; $\boldsymbol{\beta}$ is the vector of systematic effects described in Table 2; ω is the systematic regression coefficient of y_i on the ENV; $\hat{\varphi}_k$ is the ENV vector (scaled between −1 and 1) at the value k; n_{0i} and n_{1i} are the RN intercept and slope of animal i regressed on $\hat{\varphi}_k$ for the random effect n ($n \in \{u, pe, ce\}$; being u the animal genetic effect, pe the animal permanent environment

TABLE 1 Descriptive statistics of phenotypes and effects for each trait.

Traits[a]	Descriptive statistics		Effects	
	No. of records	SD	Fixed effects[b] (No. of classes)	Random effects[c]
MDP	17,085	6.37	Sex, BP, CG_G, WA (4)	a, ce
BFT	17,086	4.10	Sex, BP, CG_G, WA (5)	a, ce
WW	24,280	1.88	Sex, BP, CG_G, WA (5)	a, ce
OTW	93,494	25.63	Sex, BP, CG_G, WA (4)	a, ce
TNB	172,984	3.41	FP, CG_R, FA (11)	a, pe, ce
NBA	172,418	3.20	FP, CG_R, FA (11)	a, pe, ce
NBD	171,062	0.37	FP, CG_R, FA (11)	a, pe, ce
WN	6059	2.79	FP, CG_R, FA (11)	a, pe
IWE	121,940	4.52	FP, CG_R, FA (11)	a, pe, ce
IBF	104,917	10.08	FP, CG_R, FA (7)	a, pe
NBA_10C	154,112	3.18	FP, CG_R, FA (11)	a, pe, ce
TNB_10C	154,612	3.38	FP, CG_R, FA (11)	a, pe, ce
OTW_10C	93,460	25.90	Sex, BP, CG_G, WA (4)	a, ce
IBF_10C	95,195	10.03	FP, CG_R, FA (7)	a, pe
IWE_10C	116,787	4.45	FP, CG_R, FA (11)	a, pe, ce
NBA_15C	129,210	3.16	FP, CG_R, FA (11)	a, pe, ce
TNB_15C	129,664	3.36	FP, CG_R, FA (11)	a, pe, ce
OTW_15C	79,211	25.98	Sex, BP, CG_G, WA (4)	a, ce
IBF_15C	80,974	9.88	FP, CG_R, FA (7)	a, pe
IWE_15C	102,648	4.45	FP, CG_R, FA (11)	a, pe, ce
NBA_10CR	158.782	3.19	FP, CG_R, FA (11)	a, pe, ce
TNB_10CR	158,782	3.41	FP, CG_R, FA (11)	a, pe, ce
OTW_10CR	93,418	25.62	Sex, BP, CG_G, WA (4)	a, ce
IBF_10CR	98,421	10.13	FP, CG_R, FA (7)	a, pe
IWE_10CR	118,381	4.49	FP, CG_R, FA (11)	a, pe, ce
NBA_15CR	127,564	3.20	FP, CG_R, FA (11)	a, pe, ce
TNB_15CR	127,564	3.41	FP, CG_R, FA (11)	a, pe, ce
OTW_15CR	76,156	25.64	Sex, BP, CG_G, WA (4)	a, ce
IBF_15CR	84,946	10.12	FP, CG_R, FA (7)	a, pe
IWE_15C	100,506	4.49	FP, CG_R, FA (11)	a, pe, ce

[a]BFT, ultrasound backfat thickness (mm); IBF, interval between farrows (days); IWE, interval between wean to estrus (days); MDP, ultrasound muscle depth (mm); NBA, number of piglets born alive; NBD, number of piglets born dead; OTW, off-test weight (kg); TNB, total number of piglets born; WN, number of piglets weaned; WW, weaning weight (kg). Traits followed by _10C and _15C represents the cutoff datasets based on the temperature of 10°C (_10C) and 15°C (_15C).

[b]BP, birth parity; CG_G, growth contemporary group; CG_R, reproduction contemporary group; FA, farrowing age divided classes (number of classes inside parentheses); FP, farrowing parity; WA, weaning age divided in classes (number of classes inside parentheses).

[c]*a*, animal additive effect; *ce*, litter effect; *pe*, animal permanent environmental effect across parities.

effect and ce the common environment effect, as described in Table 2 for each trait); and e_i is the random residual for animal i. The assumptions regarding the random effects are:

$$\begin{bmatrix} u_0 \\ u_1 \end{bmatrix} \sim N\left(0, \mathbf{H} \otimes \begin{bmatrix} \sigma^2_{u_0} & \sigma_{u_0u_1} \\ \sigma_{u_0u_1} & \sigma^2_{u_1} \end{bmatrix}\right)$$

and

$$\begin{bmatrix} pe_0 \\ pe_1 \\ ce_0 \\ ce_1 \\ e \end{bmatrix} \sim N\left(0, \mathbf{I} \otimes \begin{bmatrix} \sigma^2_{pe_0} & \sigma_{pe_0pe_1} & 0 & 0 & 0 \\ \sigma_{pe_0pe_1} & \sigma^2_{pe_1} & 0 & 0 & 0 \\ 0 & 0 & \sigma^2_{ce_1} & \sigma_{ce_0ce_1} & 0 \\ 0 & 0 & \sigma_{ce_0ce_1} & \sigma^2_{ce_1} & 0 \\ 0 & 0 & 0 & 0 & \sigma^2_e \end{bmatrix}\right)$$

TABLE 2 Heritability, posterior standard deviation (SD) and Deviance Information Criterion (DIC) for each trait considering homogenous (RNM1) and heterogeneous (RNM2) residual variances.

	RNM1		RNM2		
	Heritability		Heritability		
Traits[a]	Min–max	Mean (SD)	Min–max	Mean (SD)	DIC (RNM1) – DIC (RNM2)[b]
MDP	0.27–0.31	0.29 (0.01)	0.02–0.27	0.10 (0.06)	−72.02
BFT	0.38–0.47	0.42 (0.02)	0.04–0.39	0.22 (0.07)	−56.55
WW	0.05–0.26	0.08 (0.04)	0.15–0.18	0.17 (0.01)	158.03
OTW	0.21–0.47	0.25 (0.03)	0.07–0.51	0.17 (0.06)	−441.66
TNB	0.09–0.12	0.11 (0.01)	0.01–0.11	0.04 (0.02)	−74.41
NBA	0.08–0.12	0.09 (0.01)	0.03–0.10	0.04 (0.02)	−56.54
NBD	0.04–0.09	0.06 (0.01)	0.01–0.08	0.02 (0.01)	−133.25
WN	0.07–0.31	0.08 (0.04)	0.05–0.14	0.07 (0.02)	−61.33
IWE	0.04–0.08	0.05 (0.01)	0.03–0.10	0.05 (0.01)	64.10
IBF	0.03–0.10	0.04 (0.02)	0.04–0.09	0.04 (0.01)	−376.11

[a]BFT, ultrasound backfat thickness (mm); IBF, interval between farrows (days); IWE, interval between wean to estrus (days); MDP, ultrasound muscle depth (mm); NBA, number of piglets born alive; NBD, number of piglets born dead; OTW, off-test weight (kg); TNB, total number of piglets born; WN, number of piglets weaned; WW, weaning weight (kg).

[b]Negative value means RNM1 has better fit than RNM2; Positive value means RNM2 has better fit than RNM1.

where $\sigma^2_{n_0}$, $\sigma^2_{n_1}$ and $\sigma_{n_0 n_1}$ are the variance of coefficient n_{0i}, variance of coefficient n_{1i} and covariance between n_{0i} and n_{1i}, respectively, where n represents the random effects described above (i.e. u, pe and ce), e is the residual variance, **H** is a hybrid relationship matrix containing the pedigree- and genotypic-based relationships (Aguilar et al., 2010; Christensen & Lund, 2010; Misztal et al., 2009), and **I** is an identity matrix. For RNM2, heterogeneous residual variances were used considering five classes. The classes of the residual variance for the traits that considered RH as the ENV were divided as <55, 55–60, 60–70, 70–75 and >75%. For the traits that considered MaxT as the ENV the classes were <10, 10–15, 15–23, 23–28 and >28°C. All the classes were formed based on visual inspection of the data and to show a similar frequency among them.

Variance components for the studied traits (and population) were estimated as part of a previous study (Freitas et al., 2021). Therefore, the estimation of breeding values considering RNM1 was done using fixed variance components using single-trait RNM and Bayesian inference, under a Markov chain Monte Carlo framework, with a chain length of 10,000 iterations, with burn-in and thin of 1000 and 1, respectively. For RNM2, variance components of each trait were estimated using a chain length of 600,000, burn-in of 300,000 and thin of 60. After the estimation of the variance components for RNM2, the breeding values were estimated using fixed variance components, as described for RNM1. All analyses were performed using the THRGIBBS1F90 (for RNM1) and THRGIBBS3F90 (for RNM2) software (Misztal et al., 2002). The optimal RNM for each trait was chosen based on the Deviance Information Criterion (DIC) values.

All the subsequent analyses were performed using the optimal RNM (RNM1 or RNM2). Heritability of each single value k of ENV (h^2_k) was calculated as follows:

$$h^2_k = \frac{\mathbf{\Gamma_{ukk}}}{\Sigma_i\left(\mathbf{\Gamma_{nkk}}\right) + \sigma^2_e},$$

where, $\mathbf{\Gamma_n}$ is equal $\Phi\mathbf{G_n}\Phi'$, $\mathbf{G_n}$ is the estimated (co)variance matrix between the intercept and slope terms for the corresponding n effect; Φ is a matrix of number of rows equal to the number of unique values of the ENV and two columns (a vector of "1" and the standardized ENV), $\mathbf{\Gamma_{ukk}}$ is the additive genetic variance for the ENV k, and $\mathbf{\Gamma_{nkk}}$ is the variance for the n effects (i.e., u, pe and ce) for the ENV k, and σ^2_e is the residual variance component.

2.4 | Validation parameters

Validation analyses were performed to compare the average accuracies, biases and dispersion of GEBV following the Linear Regression statistics (Legarra & Reverter, 2018), which provides a series of metrics to evaluate the predictive ability of the genomic analyses. The accuracy, bias and dispersion of genomic predictions considering the slope term were calculated following the equations:

$$\text{Accuracy} = \sqrt{\frac{\text{cov}\left(\text{GEBV}_{\text{W}}\right), \left(\text{GEBV}_{\text{P}}\right)}{\left(1-\overline{\text{F}}\right)\sigma^2_{\mathbf{u_1}}}},$$

$$\text{Bias} = \mu\left(\mathbf{u}\widehat{\text{GEBV}}_{\text{P}}\right) - \mu\left(\mathbf{u}\widehat{\text{GEBV}}_{\text{w}}\right),$$

$$\text{Dispersion} = \frac{\text{cov}\left(\text{GEBV}_{\text{W}}, \text{GEBV}_{\text{P}}\right)}{\text{var}\left(\text{GEBV}_{\text{P}}\right)},$$

where $\text{cov}\left(\text{GEBV}_{\text{W}}, \text{GEBV}_{\text{P}}\right)$ is the covariance between the GEBVs calculated using the whole (GEBV_{W}) and partial (GEBV_{P}) datasets, $\overline{\text{F}}$ is the average inbreeding, μ represents the arithmetic average function, $\mathbf{u}\widehat{\text{GEBV}}_{\text{w}}$ and $\mathbf{u}\widehat{\text{GEBV}}_{\text{P}}$ are the predicted GEBVs in the whole and partial datasets, respectively, and $\text{var}\left(\text{GEBV}_{\text{P}}\right)$ is the variance of the GEBVs in the partial dataset. The year 2018 was set as the cutoff date and all genotyped individuals born in 2018 or after that were considered as the validation population and their phenotypic records were excluded from the calculation of GEBV_{p}. In total, 2331 genotyped animals were part of the validation population and received an estimate of GEBV_{p} based on the relationship matrix.

2.5 | Use of threshold environmental variables

In addition to using the phenotypic records collected across all recorded environmental gradients, we also investigated the value of using only a partial dataset that excludes phenotypic records collected when the temperature from public weather stations was below a certain threshold that is known to not reflect the temperature of the within-barn conditions (due to the use of heating strategies). Three additional scenarios were created for the traits that considered MaxT as the ENV gradient (i.e. OTW, TNB, NBA, IBF and IWE). The scenarios were as follow: (a) all records measured when the ENV was below 10°C were excluded (named 10C); (b) all phenotypic records measured when the ENV was below 15°C were excluded (named 15C); (c) two extra scenarios were created to reflect the same number of records presented on the partial datasets (i.e. 10C and 15C). The scenarios were named 10CR and 15CR, referring to 10C and 15C, respectively. The records were randomly chosen and used to assess whether the decrease in observations from the full to the reduced dataset could be the reason for changes in the validation metrics. All the validation parameters were the same as presented previously.

In addition to the prediction metrics, the theoretical accuracy of GEBV predicted for the slope and intercept of each trait for the animal i was calculated as follows:

$$\text{TAcc}_{\text{i}} = \sqrt{1 - \frac{\widehat{\text{SD}}^2_{\text{i}}}{\left(1+\text{F}_{\text{i}}\right)\hat{\sigma}^2_{\text{u}_1}}},$$

considering $\widehat{\text{SD}_{\text{i}}}$ as the posterior standard deviation of GEBV for animal i for the RN intercept and slope, F_{i} as the inbreeding coefficient and $\hat{\sigma}^2_{\text{u}_1}$ as the estimated variance for the slope of the animal additive genetic effect (Aguilar et al., 2020). Theoretical accuracy values were compared between the whole dataset with 10C and 15C, for the intercept and slope terms of the RNM for NBA, TNB, IBF, OTW and IWE.

2.6 | Genome-wide association studies and functional analyses

The genome-wide association studies (GWAS) were carried out for the intercept and slope terms of the RNM using the postGSf90 software (Aguilar et al., 2014), considering the variance explained by moving windows of five adjacent SNP (Carvalheiro et al., 2019; Chen et al., 2021; Zhou et al., 2019). The postGSf90 software back-solves the additive genomic random regression coefficients (i.e. the GEBV for the RN intercept and slope coefficients) to SNP effects and it can be described as follows (Wang et al., 2012):

$$\hat{\mathbf{u}}_{\mathbf{0}} = \mathbf{Z}'\left(\mathbf{Z}\mathbf{Z}'\right)^{-1}\hat{\mathbf{a}}_{\mathbf{0}}$$

$$\text{and } \hat{\mathbf{u}}_{\mathbf{1}} = \mathbf{Z}^{1}\left(\mathbf{Z}\mathbf{Z}^{1}\right)^{-1}\hat{\mathbf{a}}_{\mathbf{1}}$$

where $\hat{\mathbf{u}}_{\mathbf{0}}$ and $\hat{\mathbf{u}}_{\mathbf{1}}$ are the GEBVs for the RN intercept and slope, respectively; $\mathbf{Z}$ is the matrix relating genotypes of each SNP locus. The GWAS analyses were implemented for all traits/scenarios. A threshold of 0.50% of the total genetic variance explained by each genomic window was used to define the important genomic regions associated with the traits included in this study.

Positional candidate genes were mapped using the Biomart tool (Kinsella et al., 2011) embedded in the Ensembl Genes database version 101 (http://useast.ensembl.org/index.html). Based on the start and end chromosomal positions, important genomic regions were further investigated to understand the biological processes related to the studied traits and to define the most likely functional candidate genes. Biological functions and Kyoto Encyclopedia of Genes and Genomes (KEGG) pathways (Kanehisa, 2000; Kanehisa et al., 2016, 2018) in

which the identified candidate genes are involved were assessed using the Web-based gene set analysis toolkit (WebGestalt; Liao et al., 2019). In addition, the presence of previously reported quantitative trait loci (QTL) on the identified candidate genomic regions was further investigated using the Pig QTL Database (Hu et al., 2022). GWAS and pathway studies were performed using the $GEBV_w$ for all traits and reported for the intercept and slope terms.

3 | RESULTS

3.1 | Descriptive statistics of phenotypes

The descriptive statistics after the QC for the traits using the whole range of ENV can be found in Table 1. In summary, the observations using whole records of ENV ranged from 6059 for WN to 172,984 for TNB. The descriptive statistics for the traits included on the 10C (trait abbreviation followed by "_10C") and on the 15C (trait abbreviation followed by "_15C") are shown in Table 1. In summary, the number of observations for the partial ENV ranged from 93,460 for OTW_10C to 154,612 for TNB_10C and from 79,211 for OTW_15C to 129,664 for TNB_15C. The reduction in the number of observations from the whole dataset to the partial ENV records dataset represented on average 9.10% and 21.97%, for the 10C and 15C, respectively.

3.2 | Heritability estimation and model selection

Heritability estimates and the DIC values for each trait considering RNM1 and RNM2 are shown in Table 2. Based on the DIC values, the best RNM differed by trait (Table 2): for WW and IWE the model with a heterogeneous residual variance (RNM2) provided the best fit, while the model with a homogenous residual variance (RNM1) was the best for all the remaining traits (i.e. MDP, BFT, OTW, TNB, NBA, WN and IBF). Differences in estimates of heritability had different patterns when comparing the different traits and RNM. For MDP, BFT, OTW, TNB, NBA, NBD and WN the use of heterogeneous variance presented a decrease in the range of the heritability estimates, as well as the mean value. For IWE and IBF, we only observed a small difference in the heritability estimates and for WW the use of the heterogeneous variance resulted in an increase in the heritability range, as well as on the average heritability.

TABLE 3 Validation accuracy, bias, and dispersion of genomic estimated breeding values estimated for all traits using whole records of climatic variables.

Trait[a]	Accuracy	Bias	Dispersion
BFT	0.37	−0.02	0.67
NBA	0.40	−0.02	0.75
NBD	0.41	0.03	0.90
TNB	0.35	−0.01	0.77
IBF	0.42	−0.10	0.86
MDP	0.39	−0.06	0.65
OTW	0.38	−0.36	0.82
IWE	0.36	−0.25	0.86
WN	0.27	−0.07	0.68
WW	0.29	0.13	0.60

[a]BFT, ultrasound backfat thickness (mm); IBF, interval between farrows (days); IWE, interval between wean to estrus (days); MDP, ultrasound muscle depth (mm); NBA, number of piglets born alive; NBD, number of piglets born dead; OTW, off-test weight (kg); TNB, total number of piglets born; WN, number of piglets weaned; WW, weaning weight (kg).

3.3 | Accuracies, bias, and dispersion – Whole climatic data

The validation parameters considering the whole range of ENV for the slope term (indicator of plasticity) are presented in Table 3. In general, the prediction accuracies ranged from 0.27 (WW) to 0.42 (IBF), with an average value of 0.364 (0.046) across all traits. The prediction biases ranged from −0.36 (OTW) to 0.13 (WW), and the prediction dispersion of the GEBVs ranged from 0.60 (WW) to 0.90 (NBD). Average values of the prediction bias and dispersion between all the traits were −0.073 (0.132) and 0.756 (0.097), respectively. Different to the prediction accuracy, WW was less biased when compared to OTW and IWE. The traits BFT, NBA, NBD and TNB presented the least biased results (i.e. close to zero), and prediction accuracy similar to or higher than the average of all traits. However, these traits presented very different values for the dispersion (1 is desired) of GEBVs. For all traits, the dispersion of GEBVs was lower than 1, meaning that the GEBVs for all traits were overestimated.

3.4 | Accuracies, bias, and dispersion – Reduced climatic data

The validation parameters considering the reduced range of ENV (i.e. 10C and 15C) and the randomly selected records (i.e. 10CR and 15CR) are presented in Table 4. Similar accuracy values were observed between the whole and the 10C data, except for NBA where the accuracy

TABLE 4 Validation accuracy, bias and dispersion of genomic estimated breeding values estimated for all traits using partial records of climatic variables.

	Accuracy				Bias				Dispersion			
Traits[a]	10C[b]	15C	10CR	15CR	10C	15C	10CR	15CR	10C	15C	10CR	15CR
NBA	0.37	0.31	0.35	0.32	0.01	−0.06	−0.04	0.06	0.73	0.83	0.73	0.73
TNB	0.36	0.26	0.32	0.28	0.03	0.03	0.05	0.07	0.81	0.81	0.73	0.79
IBF	0.41	0.29	0.35	0.28	−0.04	−0.13	−0.15	−0.19	0.87	1.03	0.84	0.85
OTW	0.41	0.35	0.37	0.34	−0.16	−0.20	−0.19	−0.24	0.85	0.81	0.85	0.81
IWE	0.40	0.39	0.37	0.37	−0.07	0.11	−0.15	0.11	0.79	0.73	0.73	0.74

[a]IBF, interval between farrows (days); IWE, interval between wean to estrus (days); NBA, number of piglets born alive; OTW, off-test weight (kg); TNB, total number of piglets born.

[b]10C, all records measured when the temperature was below 10°C were excluded; 15C, all records measured when the temperature was below 15°C were excluded; 10CR and 15CR, randomly sampled records to reflect the same number of records presented in the 10C and 15C, respectively.

reduced to 0.37. For the other traits, the accuracy was slightly lower (IBF) or slightly higher (TNB, OTW and IWE) than the dataset containing the complete range of ENV. In contrast, worse accuracy values were observed when using the 15C dataset, except for IWE, where the accuracy was similar to the 10C and higher than the whole range of ENV. The 10CR and 15CR were used as a comparison with the 10C and 15C, to evaluate if the change in the validation values was due to the reduction in the dataset or in the exclusion of the values below 10 or 15°C. In general, the 10CR presented lower accuracy (ranging from 0.32 to 0.37) compared to the 10C, and the 15CR presented similar accuracy values (ranging from 0.28 to 0.37) compared to the 15C.

The prediction bias for the 10C dataset had a change in signal for the NBA, from −0.02 for the whole ENV data to 0.01 for the 10C. A similar small change was observed for TNB, from −0.01 (whole ENV data) to 0.03. A reduction in bias was observed for OTW (from −0.36 to −0.16), IBF (from −0.10 to −0.04) and IWE (from −0.25 to −0.07) when comparing the whole ENV data with the 10C. The random datasets presented more biased results than the whole and reduced ENV records datasets, except for OTW.

In terms of dispersion, the 10C results were less dispersed than the 15C results, except for NBA and IBF. In addition, the datasets using the randomly selected datasets (i.e. 10CR and 15CR) were more dispersed when compared to the 10C and 15C. Finally, setting up a threshold of 10°C resulted in better prediction metrics for all the traits compared with the whole datasets, except for NBA, where a reduction in the accuracy and bias was observed when the 10°C or 15°C was used as the temperature threshold.

3.5 | Theoretical accuracies

Average theoretical accuracies for each trait are shown in Table 5. Overall, the GEBV's accuracy was greater for the intercept than for the slope term in all datasets. The largest accuracy for the intercept was observed for OTW considering the whole dataset (0.774) and the lowest was for IBF, considering the 15C dataset (0.554). Considering the slope term, the highest accuracy was observed for the whole dataset (0.630) in OTW, and the lowest was 15C (0.460) for IBF. The accuracies for the GEBV considering the different datasets within trait presented a clear distinction. The whole dataset presented the highest accuracies compared to 10C and 15C, and the 15C had the lowest accuracies for all the traits. This pattern was different when compared with the accuracies of genomic prediction (previous section), where the highest accuracy (e.g. whole data, 10C or 15C) varied depending on the trait.

3.6 | Proportion of commonly selected individuals between whole and reduced climatic data

In general, the estimates based on the 10C dataset resulted in better prediction metrics (accuracy, bias and dispersion) of GEBV, except for NBA and IBF, where the accuracy based on the whole climatic records was higher. The number of candidate individuals in the WR, 10C and 15C for the top 1%, 10% and 15% of selected individuals were evaluated, and a higher proportion of commonly selected individuals was found for the intercept in comparison to the slope term. The percentage of overlapping between animals selected as the top 1, 10 and 15% based on the estimated breeding value for the intercept and the slope terms are shown in Tables 6 and 7, respectively.

In general, considering the intercept term, the percentage of overlapping individuals was greater between the WR and 10C for all traits, being IBF the trait where the selection of the same animals in the different databases had the worst performance. The percentage of overlapping individuals selected between WR and 10C ranged

TABLE 5 Theoretical accuracies (95% confidence interval) of genomic estimated breeding value for the reaction norm intercept and slope terms considering whole and reduced datasets.

	Theoretical accuracy			
Trait[a]	Intercept[b]	Mean (95% CI)[c]	Slope	Mean (95% CI)
NBA	WR	0.764 (0.762–0.765)	WR	0.529 (0.525–0.534)
	10C	0.756 (0.754–0.757)	10C	0.498 (0.493–0.503)
	15C	0.729 (0.727–0.731)	15C	0.473 (0.467–0.478)
TNB	WR	0.774 (0.773–0.776)	WR	0.484 (0.479–0.490)
	10C	0.760 (0.759–0.762)	10C	0.512 (0.507–0.517)
	15C	0.744 (0.743–0.746)	15C	0.468 (0.462–0.473)
IBF	WR	0.594 (0.591–0.597)	WR	0.505 (0.500–0.509)
	10C	0.574 (0.570–0.577)	10C	0.489 (0.484–0.494)
	15C	0.554 (0.550–0.558)	15C	0.460 (0.455–0.466)
OTW	WR	0. 774 (0.772–0.776)	WR	0.630 (0.627–0.633)
	10C	0.752 (0.750–0.754)	10C	0.579 (0.575–0.583)
	15C	0.702 (0.699–0.704)	15C	0.514 (0.509–0.519)
IWE	WR	0.640 (0.638–0.643)	WR	0.506 (0.501–0.511)
	10C	0.609 (0.606–0.612)	10C	0.516 (0.511–0.520)
	15C	0.571 (0.567–0.575)	15C	0.479 (0.474–0.484)

[a]IBF, interval between farrows (days); IWE, interval between wean to estrus (days); NBA, number of piglets born alive; OTW, off-test weight (kg); TNB, total number of piglets born.

[b]10C, all records measured when the temperature was below 10°C were excluded; 15C, all records measured when the temperature was below 15°C were excluded; WR, datasets considering the whole temperature range.

[c]CI, confidence interval.

TABLE 6 Percentage of overlapping between animals selected as the top 1, 10 and 15% based on the estimated breeding value for the intercept term.

Intercept term									
	Top 1%			Top 10%			Top 15%		
Traits[a]	WR × 10C[b]	WR × 15C	10C × 15C	WR × 10C	WR × 15C	10C × 15C	WR × 10C	WR × 15C	10C × 15C
NBA	79.4%	68.3%	75.2%	88.2%	79.5%	82.4%	89.2%	80.9%	83.6%
TNB	79.6%	73.9%	76.2%	88.5%	82.2%	83.7%	89.1%	83.3%	84.8%
IBF	51.9%	35.2%	46.2%	68.2%	54.7%	57.9%	69.1%	58.3%	62.4%
IWE	83.4%	66.9%	68.6%	74.8%	61.2%	69.6%	76.4%	64.9%	70.4%
OTW	79.4%	46.6%	51.3%	83.0%	67.3%	71.0%	84.7%	71.0%	73.4%

[a]IBF, interval between farrows (days); IWE, interval between wean to estrus (days); NBA, number of piglets born alive; OTW, off-test weight (kg); TNB, total number of piglets born.

[b]10C, all records measured when the temperature was below 10°C were excluded; 15C, all records measured when the temperature was below 15°C were excluded; WR, datasets considering the whole temperature range.

from 51.96% (IBF) to 83.57% (IWE) for the top 1%, from 68.15% (IBF) to 88.50% (TNB) for the top 10% and from 69.05% (IBF) to 89.16% (NBA) for the top 15%. Similar to the intercept, the percentage of overlap individuals when considering the slope term was greater between the WR and 10C for all traits when considering the slope term of the regression. The trait TNB had the lowest overlap between datasets (10.89% for the top 1%), which was not the case when considering the intercept. In general, the percentage of overlapping individuals selected between WR and 10C for the slope term ranged from 10.89% (TNB) to 46.44% (OTW) for the top 1%, from 46.83% (TNB) to 56.09% (OTW) for the top 10% and from 51.44% (IWE) to 59.23% (OTW) for the top 15%.

3.7 | Genome-wide association studies

A total of 95 genomic regions were associated with the studied traits and are shown in Table 8. The Miami plots

TABLE 7 Percentage of overlapping between animals selected as the top 1, 10 and 15% based on the estimated breeding value for the slope term.

Slope term									
	Top 1%			Top 10%			Top 15%		
Traits[a]	WR × 10C[b]	WR × 15C	10C × 15C	WR × 10C	WR × 15C	10C × 15C	WR × 10C	WR × 15C	10C × 15C
NBA	36.6%	10.2%	17.6%	50.8%	29.0%	37.7%	55.1%	35.9%	45.1%
TNB	10.9%	10.9%	16.2%	46.8%	25.3%	30.7%	52.4%	31.6%	37.1%
IBF	38.0%	25.2%	26.5%	49.1%	42.0%	42.9%	52.9%	46.5%	47.8%
IWE	35.7%	19.9%	41.7%	48.7%	37.7%	46.8%	51.4%	43.1%	50.3%
OTW	46.4%	17.6%	23.1%	56.1%	38.7%	43.5%	59.2%	44.3%	49.4%

[a]IBF, interval between farrows (days); IWE, interval between wean to estrus (days); NBA, number of piglets born alive; OTW, off-test weight (kg); TNB, total number of piglets born.

[b]10C, all records measured when the temperature was below 10°C were excluded; 15C, all records measured when the temperature was below 15°C were excluded; WR, datasets considering the whole temperature range.

are presented in Figures 1–3 showing the percentage of additive genetic variance explained by a window of five adjacent SNP for the intercept and slope terms of the genomic reaction norms based on the studied traits. These genomic regions are located on most chromosomes (SSC 1, 2, 4–7, 9–18), and the maximum proportion of the additive genetic variance explained for the intercept term was 1.12% on SSC6 (BFT) and for the slope was 1.30% on SSC13 (WW). Overlapping genomic windows occurred between OTW and BFT (on SSC1), NBD and IWE (on SSC4), TNB and NBA (on SSC5), TNB, NBA and BFT (on SSC6), TNB, NBA and MDP (on SSC11), NBA and WN (on SSC12), IBF and OTW (on SSC12), IWE and MDP (on SSC13), TNB and NBA (on SSC14) and MDP and BFT (on SSC18). In general, the slope term presented more relevant regions (62 in total) compared with the intercept term (43 in total) for all the traits, except for IBF where a greater number of relevant genomic windows were found for the intercept term (5 for the intercept versus 3 for the slope). Different types of related QTL (Table 8) were found to be associated with the studied traits. Only a few of the total candidate genes were related to known biological pathways and they are shown in Table 9. Candidate genes were also related to biological regulation, metabolic process, reproduction, cell communication and proliferation, and developmental process.

4 | DISCUSSION

4.1 | Heritability estimates

Many studies have suggested that heterogeneous residual variance could improve robustness and uniformity of statistical models and positively impact livestock selection (Mulder et al., 2007, 2009). Studies in beef cattle have shown that considering heterogeneity of residual variances improved predictions for different traits related to growth and fertility in Nellore cattle under tropical conditions (Carvalheiro et al., 2019; Chiaia et al., 2015). In pigs, Chen et al. (2021) using the effect of the contemporary group as the environmental gradient in reaction norm analyses found that the use of homogeneous or heterogeneous residual variance vary among the traits. In our study, using the same Large White population as Chen et al. (2021), homogeneity (RNM1) of residual variance provided a better fit for most of the traits. For WW, as in the previously mentioned study, the use of heterogeneity (RNM2) showed a better fit. However, the heritability range was different when comparing the two studies, with Chen et al. (2021) estimating heritabilities ranging from 0.05 to 0.08, values lower than those estimated in our study (from 0.15 to 0.18). For other studied traits, such as OTW, TNB and NBA had better results with the use of RNM1, which is different from Chen et al. (2021). For OTW, for example, the estimated heritabilities of Chen et al. (2021) reached a value close to 0.70 in more extreme contemporary groups, showing that the use of homogeneity of variance may have overestimated the heritability values. An opposite pattern was observed in this study, where the use of variance heterogeneity resulted in heritability values up to 0.51.

The difference in the heritability and the better fit of residual variance may be linked to the difference between the type of environmental gradient used, since Chen et al. (2021) used the average performance of contemporary group and in our study, the environmental gradient was RH or MaxT, depending on the trait. Furthermore, these differences highlight the importance of choosing the correct environmental gradient and model in selection decisions for heat tolerance in swine breeding programs.

TABLE 8 Relevant genomic windows with the explained genetic variances, associated candidate genes and Quantitative Trait Loci (QTL).

	Genomic window[b]		Var. expl. (%)[c]			
Trait[a]	CHR	Position (bp)	Int.	Slope	Genes	Related QTLs
TNB	SSC5	69,872,903–70,055,268	**0.51**	0.04	*BID-MICAL3*	Subcutaneous adipose thickness
	SSC6	40,301,935–40,327,404	0.37	**0.77**	*ZNF536*	Litter size, intramuscular fat content, average backfat thickness
	SSC6	40,449,359–40,558,794	0.34	**0.74**	*ZNF536*	Intramuscular adipose amount, backfat between 3rd and 4th last ribs
	SSC6	40,410,621–40,491,077	0.26	**0.57**	*ZNF536*	Intramuscular adipose amount, backfat between 3rd and 4th last ribs
	SSC11	11,635,271–11,858,776	0.04	**0.55**	*NBEA-DCLK1*	Intramuscular adipose amount
	SSC11	11,688,818–11,882,898	0.05	**0.68**	*NBEA-DCLK1*	Immune capacity, social interaction
	SSC11	11,641,412–11,908,767	0.04	**0.52**	*NBEA-DCLK1*	Immune capacity, social interaction
	SSC14	4,830,393–4,905,878	0.15	**0.63**	None	Postnatal growth
	SSC14	4,850,590–4,916,999	0.15	**0.67**	None	Subcutaneous adipose thickness
	SSC14	4,880,406–4,974,128	0.18	**0.84**	None	Subcutaneous adipose thickness, sperm progressive motility
	SSC14	4,892,476–4,991,496	0.13	**0.73**	None	Subcutaneous adipose thickness
NBA	SSC4	110,658,527–110,804,173	0.02	**0.59**	*SYPL2-PSMA5-SORT1-*50,471-MYBPHL*	Postnatal growth
	SSC4	110,708,421–110,835,524	0.01	**0.54**	*PSMA5-SORT1-*50,471-MYBPHL-PSRC1-CELSR2*	Postnatal growth
	SSC5	69,770,951–70,106,805	**0.58**	0.03	*ATP6V1E1-BCL2L13-BID-MICAL3*	Subcutaneous adipose thickness
	SSC5	69,872,903–70,055,268	**0.69**	0.04	*BID-MICAL3*	Subcutaneous adipose thickness
	SSC6	40,301,935–40,327,404	**0.60**	**0.69**	*ZNF536*	Litter size, intramuscular fat content, average backfat thickness
	SSC6	40,449,359–40,558,794	**0.56**	**0.66**	*ZNF536*	Intramuscular adipose amount, backfat between 3rd and 4th last ribs
	SSC6	40,410,621–40,491,077	0.44	**0.52**	*ZNF536*	Intramuscular adipose amount, backfat between 3rd and 4th last ribs
	SSC11	11,688,818–11,882,898	0.17	**0.54**	*NBEA-DCLK1*	Immune capacity, social interaction
	SSC12	10,667,305–10,749,779	0.23	**0.51**	*KCNJ16*	Subcutaneous adipose thickness
	SSC12	10,686,572–10,763,831	0.33	**0.67**	*KCNJ16*	Subcutaneous adipose thickness
	SSC14	4,880,406–4,974,128	0.11	**0.56**	None	Subcutaneous adipose thickness, sperm progressive motility
NBD	SSC4	13,843,506–13,917,289	0.47	**0.54**	None	Subcutaneous adipose thickness, loin muscle depth, postnatal growth
	SSC4	13,872,899–13,955,717	**0.78**	**0.84**	None	Subcutaneous adipose thickness, loin muscle depth, postnatal growth
	SSC4	13,890,329–13,968,247	**0.99**	**1.01**	None	Subcutaneous adipose thickness, loin muscle depth, postnatal growth
	SSC4	13,904,769–14,019,439	**0.54**	**0.54**	None	Subcutaneous adipose thickness, loin muscle depth, postnatal growth
	SSC9	131,167,765–131,312,992	0.45	**0.50**	*DTL-INTS7*	Subcutaneous adipose thickness, response to bacterial infection

(Continues)

TABLE 8 (Continued)

Trait[a]	Genomic window[b]		Var. expl. (%)[c]			
	CHR	Position (bp)	Int.	Slope	Genes	Related QTLs
WN	SSC1	101,783,352–101,989,057	**0.53**	0.07	**51201*	Meat quality
	SSC5	52,737,350–53,148,007	**0.58**	0.01	*PDE3A*	Stillborn offspring quantity, subcutaneous adipose thickness
	SSC7	111,884,113–111,976,164	**0.53**	0.00	*KCNK13*	Subcutaneous adipose amount, postnatal growth
	SSC12	10,667,305–10,749,779	0.03	**0.63**	*KCNJ16*	Subcutaneous adipose thickness
	SSC12	10,686,572–10,763,831	0.04	**0.74**	*KCNJ16*	Subcutaneous adipose thickness
	SSC14	7,718,361–7,815,388	0.04	**0.78**	**43768-NKX3-1-NKX2-6*	Body weight
	SSC14	7,736,064–7,834,507	0.04	**0.88**	**43768-NKX3-1-NKX2-6*	Body weight
WW	SSC4	119,798,653–120,026,229	**0.54**	0.01	**45465-*45,731-DPYD*	CD8-negative leukocyte percentage, CD4-positive leukocyte percentage
	SSC10	43,164,351–43,316,559	**0.67**	0.06	*CUBN*	Average daily body weight gain, feet and leg conformation
	SSC10	43,298,783–43,339,081	**0.93**	0.05	*CUBN*	Average daily body weight gain, feet and leg conformation
	SSC13	19,334,390–19,471,344	0.03	**0.58**	*CLASP2*	Average daily body weight gain, subcutaneous adipose thickness
	SSC13	19,371,570–19,514,505	0.01	**1.01**	*CLASP2*	Average daily body weight gain, subcutaneous adipose thickness
	SSC13	19,424,219–19,553,414	0.00	**1.30**	*CLASP2*	Average daily body weight gain, subcutaneous adipose thickness
	SSC13	19,445,079–19,569,174	0.00	**0.65**	*CLASP2*	Average daily body weight gain, subcutaneous adipose thickness
IWE	SSC4	13,890,329–13,968,247	0.03	**0.56**	None	Subcutaneous adipose thickness, Loin muscle depth, postnatal growth
	SSC9	77,309,609–77,453,854	0.04	**0.70**	**45298-ASNS*	Backfat at first rib, subcutaneous adipose thickness, intramuscular fat content
	SSC9	80,130,556–80,653,760	0.05	**0.52**	**51543-NDUFA4*	Response to viral infection trait
	SSC12	4,023,403–4,121,627	**0.53**	0.03	**49848-*41,926-*46,157*	Backfat at mid-back
	SSC12	4,041,354–4,144,042	**0.70**	0.06	**49848-*41,926-*46,157*	Backfat at mid-back
	SSC12	37,811,479–37,872,427	0.00	**0.71**	**39473*	Immune response, coping behaviour
	SSC12	52,706,989–52,772,643	**0.65**	0.00	*TNK1-PLSCR3-SPEM2-TMEM102-CHRNB1-*46,700-*32,469*	Loin fat percentage
	SSC12	52,720,313–52,759,049	**0.52**	0.00	*TNK1-PLSCR3-SPEM2-TMEM102-CHRNB1*	Loin fat percentage
	SSC13	181,648,992–182,171,751	0.13	**0.54**	**41861-*43,148-*44,161-*50,489-CXADR-*21,535*	Feed conversion ratio, maternal infanticide
	SSC13	181,970,420–182,109,345	0.18	**0.68**	**44161-*50,489-*44,161-*50,489*	Feed conversion ratio
	SSC13	182,071,628–182,230,243	0.17	**0.61**	*CXADR-*21,535-*41,266-BTG3*	Feed conversion ratio
	SSC15	138,004,767–137,874,381	**0.57**	0.09	None	Gestation length, total number born alive
	SSC15	137,903,104–138,141,908	**0.59**	0.12	*TRAF3IP1-ASB1-*42,914*	Gestation length, total number born alive

TABLE 8 (Continued)

Trait[a]	Genomic window[b]		Var. expl. (%)[c]		Genes	Related QTLs
	CHR	Position (bp)	Int.	Slope		
IBF	SSC2	114,613,136–115,034,260	0.00	**0.68**	*PJA2-MAN2A1-*46,792-*43,955-*50,918*	Disease susceptibility
	SSC2	114,753,838–115,226,553	0.00	**0.94**	*MAN2A1-*46,792*	Disease susceptibility
	SSC2	114,929,978–115,148,681	0.00	**0.52**	**46792-*43,955-*50,918*	Disease susceptibility
	SSC5	80,009,588–80,103,444	**0.60**	0.31	*CHST11*	Loin weight
	SSC5	80,020,474–80,176,521	**0.62**	0.31	*CHST11-*49,056-TXNRD1*	Loin weight
	SSC12	10,667,305–10,749,779	**0.59**	0.29	*OSBPL7-MRPL10-LRRC46-SCRN2-SP6*	Subcutaneous adipose thickness
	SSC12	10,686,572–10,763,831	**0.72**	0.38	*OSBPL7-MRPL10-LRRC46-SCRN2-SP6*	Subcutaneous adipose thickness
	SSC12	24,026,238–24,132,022	**0.59**	0.11	None	Disease susceptibility, ovary weight
OTW	SSC1	52,110,037–52,241,222	**0.54**	0.02	*RIMS1-RIMS1*	Body weight at weaning
	SSC12	10,686,572–10,763,831	0.00	**0.58**	*DNAH9*	Subcutaneous adipose thickness
MDP	SSC11	11,635,271–11,858,776	**0.66**	**0.68**	None	Intramuscular adipose amount
	SSC11	11,688,818–11,882,898	**0.83**	**0.82**	None	Immune capacity, social interaction
	SSC11	11,641,412–11,908,767	**0.63**	**0.61**	None	Immune capacity, social interaction
	SSC12	56,141,634–56,240,724	**0.78**	0.01	None	Average backfat thickness, intramuscular adipose amount
	SSC12	56,124,653–56,285,163	**0.57**	0.02	None	Average backfat thickness, intramuscular adipose amount
	SSC12	56,197,640–56,304,422	**0.58**	0.01	None	Average backfat thickness, intramuscular adipose amount
	SSC13	181,970,420–182,109,345	0.23	**0.54**	None	Feed conversion ratio
	SSC13	182,071,628–182,230,243	0.23	**0.56**	None	Feed conversion ratio
	SSC16	30,711,806–30,827,133	**0.61**	0.18	None	Feed conversion ratio, backfat at last lumbar
	SSC16	30,756,112–30,879,331	**0.61**	0.18	None	Feed conversion ratio, backfat at last lumbar
	SSC16	30,770,873–30,879,505	**0.53**	0.16	None	Feed conversion ratio, backfat at last lumbar
	SSC18	42,098,956–42,011,351	0.26	**0.56**	None	Abdominal fat weight, body weight
	SSC18	42,078,870–42,126,037	0.41	**0.94**	*MINDY4-MINDY4*	Abdominal fat weight, body weight
	SSC18	42,038,739–42,133,494	0.36	**0.84**	*GHRHR-AQP1-MINDY4*	Abdominal fat weight, body weight
	SSC18	42,050,154–42,139,490	0.25	**0.61**	*AQP1-MINDY4*	Abdominal fat weight, body weight

(Continues)

TABLE 8 (Continued)

Trait[a]	Genomic window[b] CHR	Position (bp)	Var. expl. (%)[c] Int.	Slope	Genes	Related QTLs
BFT	SSC1	52,025,432–52,217,817	0.40	**0.76**	*RIMS1*	Meat quality
	SSC1	52,110,037–52,241,222	**0.53**	1.00	*RIMS1*	Body weight at weaning, immune response
	SSC1	52,165,770–52,262,327	0.37	**0.70**	*RIMS1*	Feed conversion ratio
	SSC1	52,196,681–52,284,040	0.30	**0.57**	*RIMS1*	Feed conversion ratio
	SSC6	40,261,946–40,361,536	**0.56**	0.09	*ZNF536*	Intramuscular adipose amount, subcutaneous adipose thickness
	SSC6	40,301,935–40,327,404	**1.12**	0.19	*ZNF536*	Litter size, Intramuscular fat content, Average backfat thickness
	SSC6	40,449,359–40,558,794	**1.09**	0.18	*ZNF536*	Intramuscular adipose amount, Backfat between 3rd and 4th last ribs
	SSC6	40,410,621–40,491,077	**0.88**	0.15	*ZNF536*	Intramuscular adipose amount, backfat between 3rd and 4th last ribs
	SSC7	17,654,533–17,780,731	0.32	**0.72**	**50045-*50,747-*01083-*46,828*	Backfat between 6th and 7th ribs, social interaction, postnatal growth
	SSC7	17,665,901–17,805,259	0.36	**1.04**	**50045-*50,747-*01083-*46,828-*48,107-*50,980*	Backfat between 6th and 7th ribs, social interaction, postnatal growth
	SSC7	17,707,473–17,835,129	0.35	**1.28**	**46828-*48,107-*50,980*	Backfat between 6th and 7th ribs, social interaction, postnatal growth
	SSC7	17,753,072–17,861,661	0.17	**0.68**	**46828-*48,107-*50,980-*46,227-*47,419*	Backfat between 6th and 7th ribs, social interaction, postnatal growth
	SSC7	18,206,338–18,307,182	0.08	**0.56**	None	Backfat between 6th and 7th ribs, Loin muscle area
	SSC17	7,420,959–7,523,628	**0.66**	0.37	**45345*	Body weight at weaning
	SSC17	7,436,131–7,546,880	**0.55**	0.31	**45345*	Body weight at weaning
	SSC18	42,078,870–42,126,037	**0.52**	**0.59**	None	Abdominal fat weight, body weight

[a]BFT, ultrasound backfat thickness (mm); IBF, interval between farrows (days); IWE, interval between wean to estrus (days); MDP, ultrasound muscle depth (mm); NBA, number of piglets born alive; NBD, number of piglets born dead; OTW, off-test weight (kg); TNB, total number of piglets born; WN, number of piglets weaned; WW, weaning weight (kg).

[b]Genomic windows are defined by the five adjacent SNPs that explained 0.5% or more of the total additive genetic variance; Chr, chromosome; positions refer to Sscrofa11.1.

[c]Explained genetic variances in percent for intercept and slope by five adjacent SNPs; explained variances with ≥0.5% are denoted in bold.

4.2 | Validation metrics

Among the components that are part of the selection response of a trait in a population (i.e. accuracy, selection intensity, genetic standard deviation of the trait and generation interval), accuracy is one of the most important (Falconer et al., 1996). Thus, improving breeding value accuracies is critical to increase the rate of genetic gain. Furthermore, biased predictions can lead to incorrect comparisons between animals of different generations and inaccurate estimates of genetic trends (Legarra & Reverter, 2018). Despite the complexity of the statistical models used, validation accuracy values of each studied trait were in agreement with the literature. One of the factors that influence the accuracy of genomic predictions relies on the heritability of the trait (Meuwissen et al., 2001), where traits with higher heritability are expected to have higher prediction accuracies. This relationship was not the case in most of the studied traits, since traits with low heritability (e.g. TNB and NBA) presented higher accuracies when compared with more heritable traits (e.g. OTW and BFT). This unexpected relationship may be related to other factors, such as that TNB and NBA have repeated measures while OTW and BFT have only one record per animal. Nevertheless, greater accuracies are possible by increasing the numbers of both genotyped and phenotyped animals.

The genomic prediction accuracies observed in our study were within the range of other studies in the literature. Fangmann et al. (2017) estimated prediction accuracies of 0.45 ± 0.11 for NBA in Large White pigs using the ssGBLUP method. Low prediction accuracy (0.26 ± 0.12) was reported by Hidalgo et al. (2015) for TNB in Large White pigs. Prediction accuracies of BFT were estimated to be 0.39 ± 0.03, 0.52 ± 0.03 and 0.44 ± 0.04 for Duroc, Landrace and Yorkshire populations (Salek Ardestani et al., 2021). Furthermore, the bias values showed that most of the studied traits presented under-estimated GEBVs. For some traits, this result was different from what is found in the literature. For instance, Salek Ardestani et al. (2021) estimated the regression coefficient of genomic prediction (which is comparable with the dispersion from the LR method) and found the GEBVs for BFT to be over-estimated, with values of 1.60 ± 0.13, 1.14 ± 0.08 and 1.31 ± 0.13 for Duroc, Landrace and Yorkshire populations, respectively. In addition, Fangmann et al. (2017) estimated a value of 0.99 ± 0.27 for the regression coefficient of genomic prediction for NBA using the ssGBLUP method. The differences in the genomic prediction metrics for the same traits are mainly due to differences in the statistical model, validation methods and factors related to the population, as described previously (e.g. differences in the estimated trait heritability, single or repeated records, population structure and genetic diversity of the population).

Change in the prediction metrics was observed when excluding the data collected when the outside barn temperatures were below 10°C or 15°C. Because the environmental gradient used was derived from climatic records from public weather station, such environmental data may not represent the actual range of temperature found inside the barn due to mitigation strategies that producers implement (Mayorga et al., 2019). Removing these records resulted in better, or similar, predictions for most of the traits. Predictions using the 10C database presented the best values. This was also observed in relation to the theoretical accuracy of the GEBVs. Considering the phenotypic records measured when the ENV values (from public weather stations) were below the threshold of 10°C and 15°C as missing records, resulted in similar accuracies as in the 10CR and 15CR. However, the increase in bias suggests that considering the exclusion of values below the thresholds may be a better option. To verify if changes in the prediction values were due to a decrease in the number of phenotypic records, datasets containing the same number of records as 10C and 15C were evaluated, and in all scenarios these random datasets performed worse than the datasets that had records removed below 10°C or 15°C. The better results observed using the 10C dataset (as compared to 10CR) may be related to the presence of genotype by environment interaction effects that the model is able to capture when the temperature is above 10°C, however, is unable to predict when the temperature is below this threshold.

The GEBV estimation for the intercept term was more accurate than for the slope term, as expected. Furthermore, for the intercept, the use of all data resulted in greater accuracy of the GEBVs. This can be explained since the estimation of the intercept term expresses the overall performance in average ENV. Therefore, having more records (i.e. by not excluding data below the threshold) will result in better estimates. However, for the slope term, having more records did not result in a better (i.e. more accurate) estimation of the GEBVs for TNB and IWE. Once again, this pattern may be related to the presence of GxE interaction effects that the model is able to capture when the temperature is above 10°C and not when it is below 10°C. Nevertheless, this relationship should be evaluated in further studies, and the results should be compared with predictions made using in-barn climatic data, which remains the gold standard for the evaluation of HS conditions in pig farms (Freitas et al., 2023; Johnson et al., 2023).

The percentage of overlapping individuals selected between the data set considering all climatic records (WR) and each of the datasets considering the thresholds of 10°C and 15°C (i.e. 10C and 15C, respectively) varied

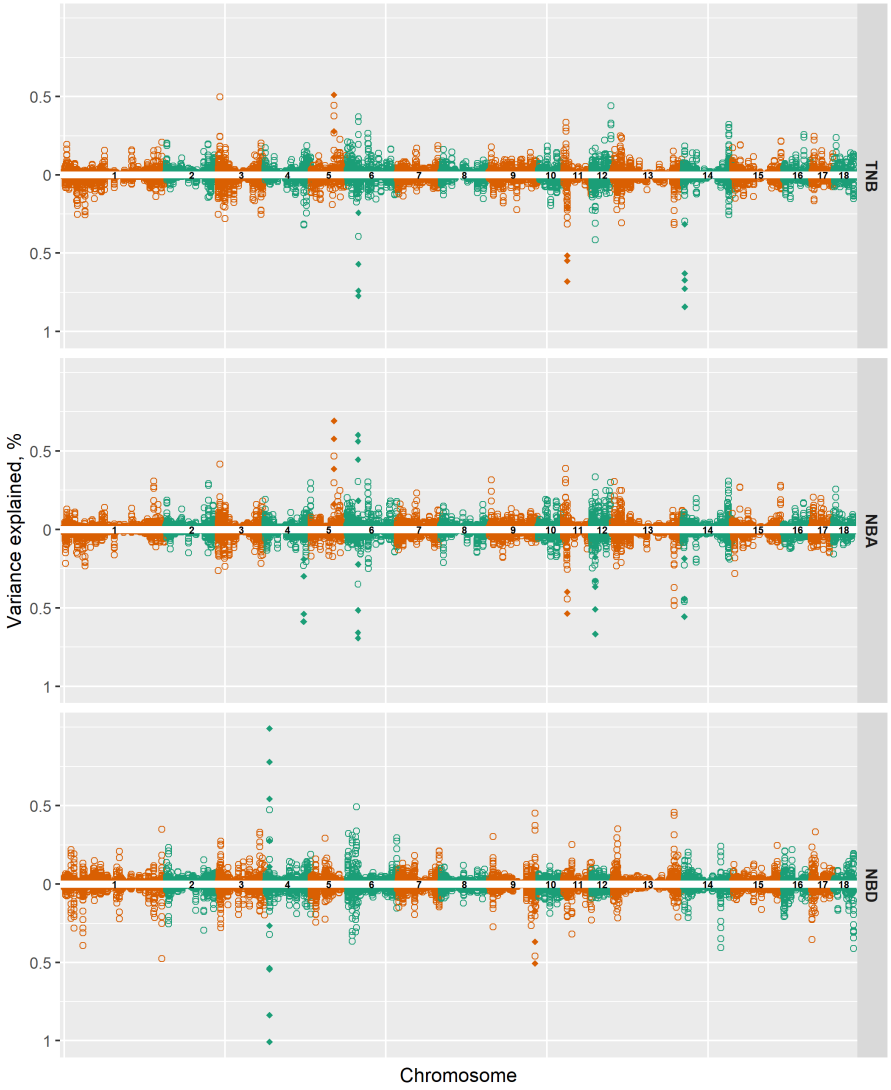

FIGURE 1 Miami plots for the proportion of the total additive genetic variance explained by 5-SNP sliding genomic windows. The intercept and slope terms of the reaction norm model are placed on the upper and lower arms of the y-axis, respectively; each open dot represents a SNP, while all SNPs within the relevant genomic windows are denoted as solid diamonds. NBA, number of piglets born alive; NBD, number of piglets born dead; TNB, total number of piglets born.

depending on the number of selected individuals. This number was higher for the intercept term compared to the slope term. This has direct consequences, since the selection of animals considering the G × E interaction for heat tolerance is performed based on the predicted GEBVs for the slope term (which indicates plasticity). The fact that the overlap of animals selected from each of the datasets is low when considering G × E shows the importance of using the most accurate environmental information (i.e. in-barn climatic records). Future studies should be carried out to compare the use of reduced environmental data with climatic measurements from within the barn.

For most of the traits, similar percentages of overlapping animals were observed. However, IBF had the lowest percentage of commonly selected animals between the datasets (considering the top 1, 10 or 15%). This low number of commonly selected individuals might be directly related to the theoretical accuracies of GEBVs, where IBF had the smaller accuracies compared with the remaining traits. For TNB, considering the top 1% of selected individuals, the percentage of commonly-selected animals for the slope term had a lower performance compared with the other traits and may be a direct indication of the low prediction accuracy and under-dispersion of the GEBVs. Once again, this indicates the need to use more accurate information about the ENV that the animals are being raised.

4.3 | Genome-wide association studies

This study supports the polygenic nature of HS, with many regions across the genome making small contributions to the total genetic variation of each complex trait. In this study, we observed that most of the candidate genomic windows (~60%) are involved in environmental sensitivity, as they are associated with the RNM

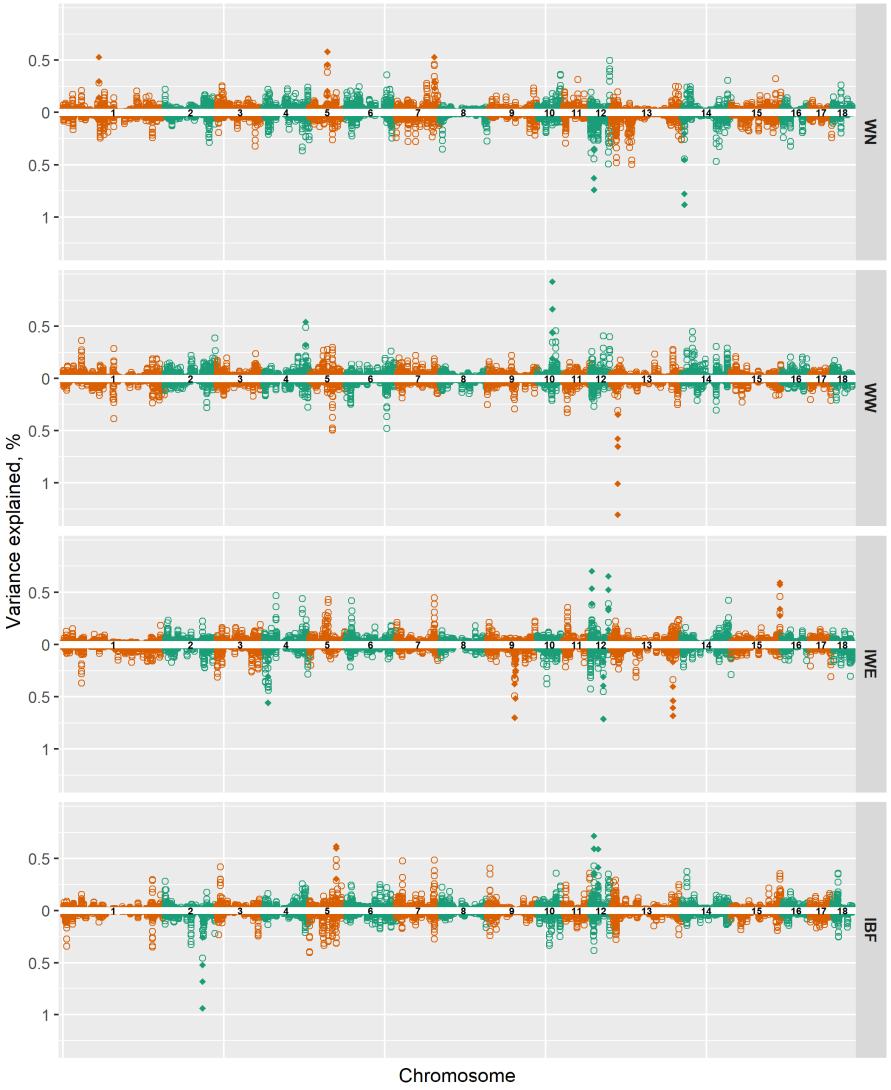

FIGURE 2 Miami plots for the proportion of the total additive genetic variance explained by 5-SNP sliding genomic windows. The intercept and slope terms of the reaction norm model are placed on the upper and lower arms of the y-axis, respectively; each open dot represents a SNP, while all SNPs within the relevant genomic windows are denoted as solid diamonds. IBF, interval between farrows (days); IWE, interval between wean to estrus (days); WN, number of piglets weaned; WW, weaning weight (kg).

slope. In addition, the differences when considering the intercept and the slope show that different genomic regions have a greater or smaller effect depending on the environment.

Several candidate genes were identified but only a few of them were previously reported in other pig studies. The gene *MICAL3* located on SS5 for the intercept term for NBA and TNB were also reported by Chen et al. (2021) for NBA when studying G × E in the same population using the effect of the contemporary group as the environmental gradient. This gene was previously reported to be associated with immune response traits in Canadian Holstein cattle (Thompson-Crispi et al., 2014), and with sperm quality in pigs (Gòdia et al., 2020). Interestingly, the gene *ZNF536*, identified to be related to the slope term for TNB, NBA and BFT, seems to have an opposite effect on these traits. The SNPs located on the genomic window that *ZNF536* was identified have a positive effect on TNB and NBA, while the effect is negative on BFT. The *ZNF536* gene was previously reported to be in strong positive selection in the Chantecler chicken, a dual-purpose breed from Canada adapted to cold weather (Xu et al., 2021). This gene was reported to have an important role in the development of forebrain neurons involved in social behaviour and stress (Thyme et al., 2019).

A GWAS study for social genetic effects and direct genetic effects on growth in Landrace pigs (Hong et al., 2020) found the gene *RIMS1* to be a candidate gene for average daily gain. In our study, this gene was also related to the intercept and slope term for a growth trait (OTW), and with BFT. Like the *ZNF536* gene, the RIMS1 and the biological pathways it is involved with (e.g. Synaptic vesicle cycle and retrograde endocannabinoid signalling), have a role in behaviours linked to schizophrenia (Tansey et al., 2014). The *DPYD* was found to be a candidate gene for WW (related to the intercept term). Previous studies reported this gene to be related to intramuscular fat in Duroc pigs (Ding et al., 2019) and marbling in beef (Lim et al., 2014). The

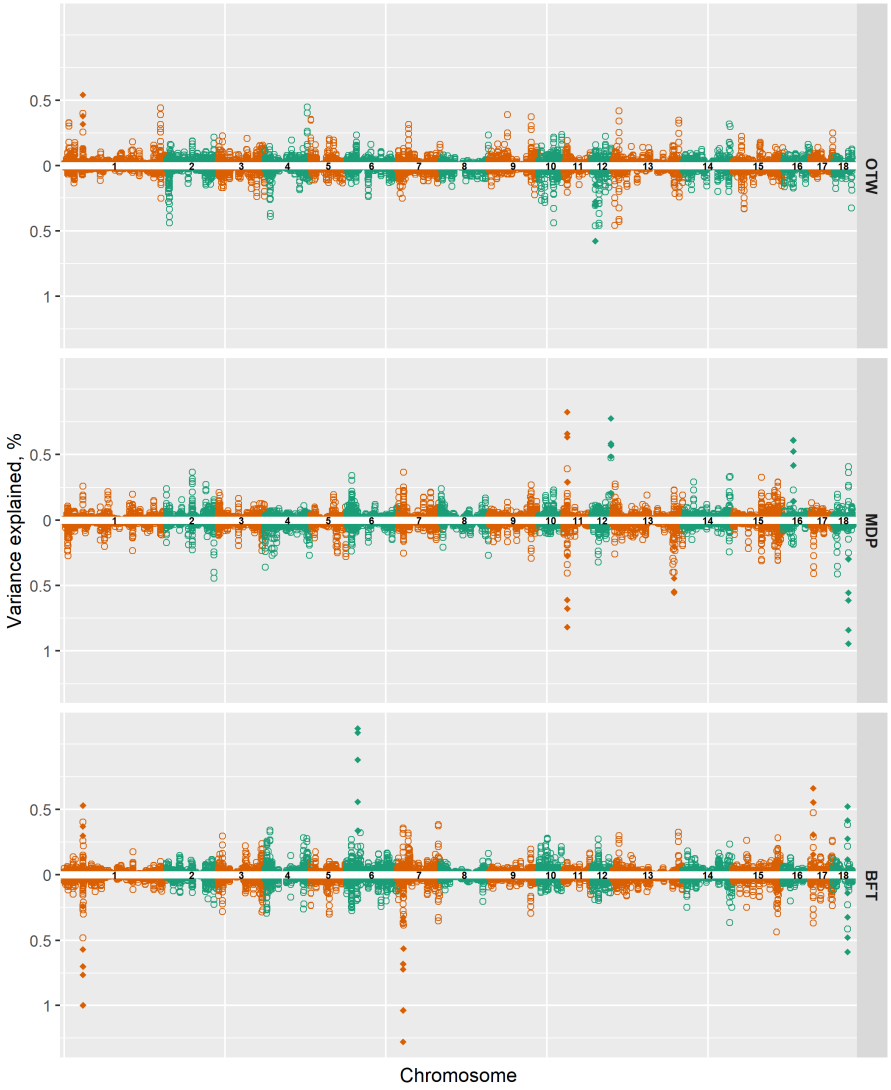

FIGURE 3 Miami plots for the proportion of the total additive genetic variance explained by 5-SNP sliding genomic windows. The intercept and slope terms of the reaction norm model are placed on the upper and lower arms of the y-axis, respectively; each open dot represents a SNP, while all SNPs within the relevant genomic windows are denoted as solid diamonds. BFT, ultrasound backfat thickness (mm); MDP, ultrasound muscle depth (mm); OTW, off-test weight (kg).

TABLE 9 Biological pathways of selected genes for the studied traits.

Pathway	Gene symbol	*p* value
Viral myocarditis	*CXADR*, *BID*	0.011911
Synaptic vesicle cycle	*RIMS1*, *ATP6V1E1*	0.013118
Renin secretion	*PDE3A*, *AQP1*	0.014807
Selenocompound metabolism	*TXNRD1*	0.047976
Pantothenate and CoA biosynthesis	*DPYD*	0.053474
Oxidative phosphorylation	*ATP6V1E1*, *NDUFA4*	0.054816
Glycosaminoglycan biosynthesis	*CHST11*	0.056211
Proximal tubule bicarbonate reclamation	*AQP1*	0.061663
Vitamin digestion and absorption	*CUBN*	0.061663
Retrograde endocannabinoid signalling	*RIMS1*, *NDUFA4*	0.064728

fact it was involved with WW might indicate that during the weaning stage, the *DPYD* gene may be involved in weight gain in piglets. Another interesting gene is the *CHST11*, found to be related to the intercept term of IBF. This gene was previously reported to be related to IBF in different parities of Landrace and Large White pigs (Wu et al., 2019), and with prolificacy in sheep and goats (Tao et al., 2021). Although relevant genes have been identified for all traits, additional studies should prioritize specific genes for more in-depth studies for validation purposes.

5 | CONCLUSIONS

The genomic background of heat tolerance in Large White pigs based on economically important traits was explored in the present study. Our results indicated that accurate genomic predictions for heat tolerance based on the single-step RNM can be obtained. Models using homogeneous residual variance presented a better fit for most of the traits (MDP, BFT, OTW, TNB, NBA, WN and IBF), while for WW and IWE, heterogeneous residual variance had a better fit. Based on the studied traits, using only phenotypic records collected when the outside temperature (from public weather stations) was above 10°C provided better predictions for most of the traits. However, simulation studies where true breeding value are known should be conducted in future studies and within-barn climatic data should be collected to enable a better comparison and validation of these scenarios. Genomic windows and candidate genes were identified, which contributes to a better understanding of the genomic architecture of heat tolerance in pigs and will be of great value for the implementation of genomic selection for heat-tolerant pigs.

AUTHOR CONTRIBUTIONS

LFB and PHF conceived, designed and coordinated this research. PHF performed the data analyses and wrote the first version of the manuscript. YH provided all the datasets. PHF, LFB, JSJ, FT, APS, and YH provided technical assistance and suggestions in the final version of the manuscript. All authors read and approved the final manuscript.

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CONFLICT OF INTEREST STATEMENT

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

DATA AVAILABILITY STATEMENT

The phenotypic and genomic data used in this study are property of the industry partner that contributed to the study and therefore are not readily available due to their commercial sensitivity.

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