https://doi.org/10.22319/rmcp.v16i2.6731

Technical note

Detection of selection signals in Mexican hairless pigs

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Abstract:

The Mexican hairless pig (MHP) is a subpopulation of creole pigs characterized by being hardy and resistant to diseases and having a high quality of meat, which gives it outstanding genetic qualities. Signals in the genome, derived from genetic selection, can be used to associate with genes and quantitative trait loci (QTL). The present study aimed to determine if there are selection signals (SSs) in the MHP genome, as well as to associate candidate genes (CG) and QTL with regions showing SS. A total of 107 pigs were genotyped with the GGP Porcine 50k BeadChip, and SSs were determined using the integrated haplotype score (iHS) method, with which significant SSs (P<0.0001) were observed in 20 markers distributed on chromosomes 3, 5, 6, 7, 8, 16, and 17. Chromosome 8 presented greater conservation and intensity, with possible association with response to selection in recent generations; small, less delimited haplotypes were observed on chromosomes 3 and 7 as an indicator of natural selection or adaptation. CGs were related to characteristics associated with the immune system, adaptation, behavior, obesity, embryonic implantation and development, meat quality, growth, development, and feed efficiency. One hundred forty-six (146) QTL were associated, which are related to behavior, conformation, fatness, immune capacity, and reproduction. There are SSs in the MHP, which can be used in genetic conservation and improvement programs.

Keywords: QTL, Candidate genes, Animal genetic resources, Creole breeds, SNP.

Received: 18/06/2024

Accepted: 14/01/2025

The Mexican hairless pig (MHP) is a subpopulation of creole pigs[1]; its origin dates back to the colonization of the American continent. In Europe, the genetic bases of the pig are attributed to four lines: Celtic, Iberian, Neapolitan, and Asian[2,3]. The establishment and distribution throughout the American continent was transcendent due to the genotype-environment interaction[4]; the effects of selection, regulated by humans and the environment, have generated different breeds and lines with their productive and functional particularities[5,6]. The MHP is a reservoir of genetic material[3], with high hardiness, adaptation to adverse climates, and resistance to diseases; it moves long distances in hostile terrain and with scarcity of food[7,8,9]; in addition, it has good quality meat due to the intramuscular fat it deposits[10].

Patterns of genetic variation provide information about genetic mechanisms associated with adaptation and production traits. Gene expression plays an important role during the course of domestication and evolution; deciphering the underlying selection mechanisms not only benefits conservation and breeding but also impacts the identification of genes associated with biological processes and productive and reproductive traits of interest[11]. Selection processes leave their mark on the genome, such as reduced genetic diversity and the existence of haplotypes[12]. Genomics applications, based on high-density sequencing, have made it possible to identify selection signals, characterizing natural and artificial selection events[5,13]. Selection signals (SS) are assumed with the detection of genomic regions that present genetic variants exposed to a rapid increase in allele frequencies given selection pressure, or the determination of fixed genomic regions in a population with established phenotypes[5].

Haplotype-based statistics detect a rapid increase of a selected allele at a medium frequency during which the range of haplotype association is not lost by recombination[14]. Genome exploration in search of SS has detected signals from candidate genes associated with phenotypic variables and traits of economic interest[15]. Given the relevance of the MHP as a genetic resource with adaptation and hardiness qualities, as well as productive potentials, the objectives of this study were to identify the possible SSs and to associate candidate genes (CG) and quantitative trait loci (QTL) with the regions that show selection.

The genotypes analyzed belonged to 107 MHPs sampled in 12 production units under the backyard and extensive systems, located in the states of Yucatán, Campeche, and Quintana Roo. The sampled pigs meet the specifications of the MHP breed pattern and are derived from the genealogical registry of the Mexican Association Specialized in Creole Pigs[16]. The genotypes make up the panel of 50657 SNP (single nucleotide polymorphisms) integrated into the GGP Porcine 50K BeadChip. SNP with minor allele frequency (MAF) below 0.05 and genotyping rate below 0.90 were discarded, as were individuals with more than 10 % of missing genotypes. After editing, the missing genotypes were imputed, forming haplotypes due to linkage disequilibrium with the SHAPEIT v.2 software[17]. The CMplot[18] library of R was used to generate the position graph of SNP in the pig genome *Sus scrofa* 10.2, according to their location through chromosomes. The integrated haplotype score[19] (iHS) method was used for detecting SSs, which is a variant of the haplotype homozygosity (EHH)[20] method. The iHS requires the presence of the ancestral allele; it identifies positive selections since the frequency of the derived haplotype is increased. The analysis was performed with the rehh 2.0 library of the R[21] package; the test statistic was generated from the following equation:

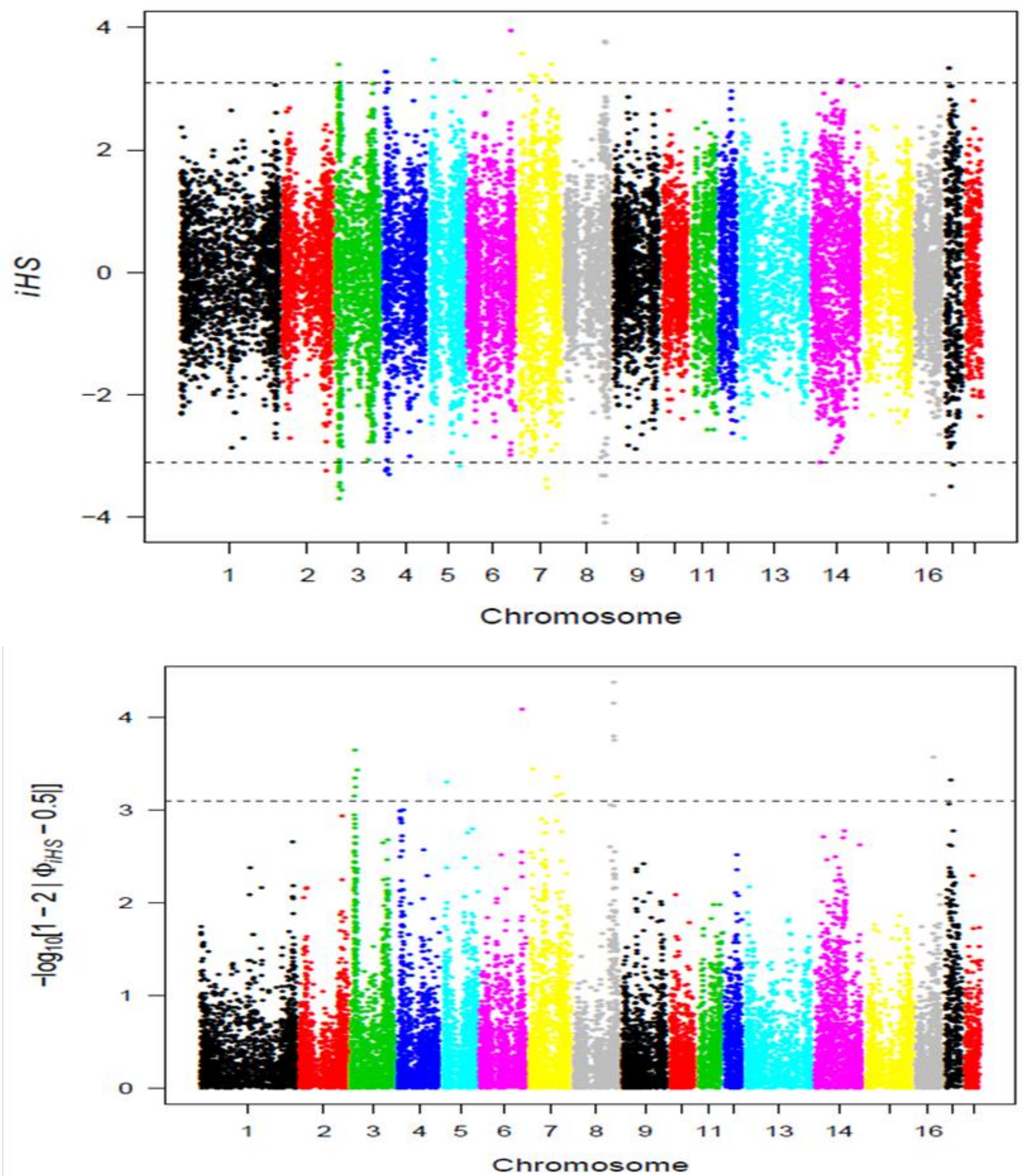
$$iHS(s) = \frac{\log\left(\frac{iHHa}{iHHd}\right)(s) - \mu\, ps\, [\log\left(\frac{iHHa}{iHHd}\right)]}{\sigma\, ps\, [\log\left(\frac{iHHa}{iHHd}\right)]}$$

Where: iHS(s), integrated haplotype score; iHHa, area under the extended haplotype homozygosity curve for ancestral alleles; iHHd, area under the extended haplotype homozygosity curve for derived alleles; μ^{ps}, standardization mean, calculated on all SNPs with derived allele frequency (*ps*) similar to that of the SNP nucleus (*s*); σ^{ps}, standard deviation of standardization, calculated on all SNPs with derived allele frequency (*ps*) similar to that of the SNP nucleus (*s*). After standardizing the data, the piHS transformation was performed based on the equation $piHS = -\log10\,(1 - 2|\Phi\,(iHS) - 0.5|)$; where: $\Phi\,(x)$ represents the Gaussian cumulative distribution function.

SNPs have an approximation to the neutral distribution and piHS is interpreted as a probability value (Pval; on a scale - log10) associated with the neutral hypothesis of non-selection; markers that expressed a Pval<0.0001 were taken as significant and as presenting selection signals. Ancestral alleles derived from the study by Bianco *et al*[22] were used, where they report a catalog of autosomal variations of a single nucleotide using four *Sus* species (*Sus barbatus*, *Sus celebensis*, *Sus verrucosus*, and *Sus cebifrons*) and one *Phacochoerus* species (African warthog) as an external group. The pegas library of the R[23] package was used to plot the haplotypes derived from the linkage disequilibrium of the chromosomes with the highest number of markers with significance before the selection signal. Markers with significant SS (Pval<0.0001) were used to associate CGs with QTL by aligning positions using the Genomic Ranges library of the R[24] package, which is based on assigning each SNP to all genes partially or completely located in a region of 0.75 Mb around each locus, based on references published in the NCBI (National Center for Biotechnology Information) and the EBI (European Bioinformatics Institute). The BiomaRt library of the R[25] package was used to access the Ensembl database and perform the overlap of candidate genes with the regions that indicated SSs. The information on the QTLs was consulted in the Pig QTLdb database[26].

After the editing process, the iHS was estimated for 33499 SNP. Figure 1 shows the genomic markers or regions that show significant selection signals ($P<0.0001$) and the iHS and piHS distributed across the various chromosomes. The result showed a decrease in haplotypic homozygosity on a locus based on the comparison between the derived and ancestral allele within a given population; extreme values of iHS (negative or positive) denote excessive haplotypic homozygosity on ancestral or derived alleles, such that genomic regions that present iHS peaks in one or both directions are important because they have undergone selection.

Figure 1: Manhattan plots with values of iHS haplotypes (integrated haplotype score), haplotypes, and the piHS transformation [piHS = − log10 (1 − 2|Φ (iHS) − 0.5|]



Values that exceed the dotted line indicate statistical significance (*P*<0.0001).

There were 20 markers that showed significance (*P*<0.0001) to the SS (Table 1), distributed on chromosomes 3, 5, 6, 7, 8, 16, and 17.

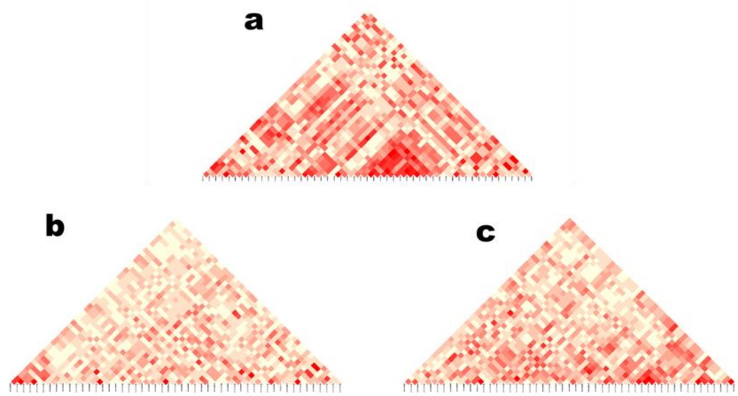
Table 1: Statistically significant SNP markers (*P*<0.0001) in genomic regions with selection signals

SNP	CHR	Position (bp)	iHS	piHS	*P*-value
WU_10.2_8_128404843	8	128404843	-4.094	4.373	4.24E-05
WU_10.2_8_128418568	8	128418568	-3.976	4.154	7.01E-05
ASGA0096926	6	134750885	3.941	4.090	8.13E-05
WU_10.2_8_128447508	8	128447508	3.776	3.797	1.59E-04
WU_10.2_8_128761047	8	128761047	3.753	3.757	1.75E-04
WU_10.2_3_14556426	3	14556426	-3.690	3.649	2.25E-04
WU_10.2_16_59651156	16	59651156	-3.645	3.574	2.67E-04
WU_10.2_7_12543606	7	12543606	3.568	3.445	3.59E-04
MARC0081434	3	21071325	-3.563	3.436	3.66E-04
WU_10.2_7_88718236	7	88718236	-3.514	3.355	4.42E-04
ASGA0013651	3	15463031	-3.509	3.347	4.50E-04
WU_10.2_17_27206748	17	27206748	-3.493	3.320	4.78E-04
WU_10.2_5_10602026	5	10602026	3.483	3.304	4.96E-04
WU_10.2_3_16123577	3	16123577	-3.446	3.245	5.69E-04
MARC0106494	7	101800928	3.405	3.179	6.63E-04
WU_10.2_3_13551908	3	13551908	3.390	3.155	7.00E-04
ALGA0042950	7	87847151	-3.385	3.148	7.12E-04
ASGA0075836	17	21585923	3.332	3.064	8.62E-04
WU_10.2_8_118363092	8	118363092	-3.327	3.056	8.79E-04
WU_10.2_8_128287306	8	128287306	-3.319	3.044	9.04E-04

SNP= reference name of the SNP; CHR= chromosome of *Sus scrofa*; Position (bp) = base pairs; iHS= integrated haplotype score; piHS= integrated haplotype score transformed.

The haplotypes of chromosomes with the presence of markers with selection are shown in Figure 2; chromosome 8 presented greater conservation and intensity, with possible association with response to selection in recent generations; on chromosomes 3 and 7, small, less delimited haplotypes were observed as an indicator of natural selection or adaptation.

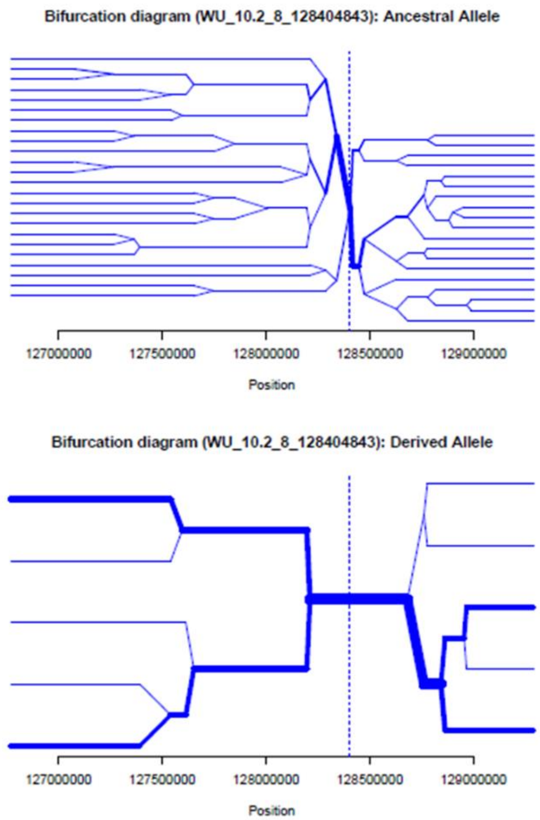
Figure 2: Haplotypes of significant chromosomes: a) chromosome 8; b) chromosome 7; c) chromosome 3



The abscissa axis represents the loci where the linkage disequilibrium is being measured; the vertical axis represents the contrast loci with which the linkage disequilibrium was measured. The value within each cell (heat map; color intensity) represents the value of the linkage disequilibrium (r^2= 0 to 1) among the corresponding loci; a higher intensity in color shows disequilibrium (the alleles in those loci will be inherited together); a low intensity indicates that the loci are independent.

Figure 3 shows the structure of haplotypes around the central allele (WU_10.2_8_128404843) with the highest piHS (*P*<0.00005). The bidirectional diagram allow to interpret the origin of an SS; it plots the breakdown of LD at increasing distances from the central allele in the selected focal SNP. The root (focal SNP) of the diagram is the central allele and is identified by a vertical dotted line. The diagram is bidirectional and represents the centromere-proximal LD and the distal centromere. In one direction, each marker is an opportunity for a node, the diagram splits or not depending on whether both or only one allele is present; the LD breakdown in the background of the central haplotype is represented at progressively longer distances. The thickness of the lines corresponds to the number of individuals with the indicated long-distance haplotype, the greater the number of individuals, the greater the thickness[21].

Figure 3: Haplotype structure (position in base pairs) around the central allele (WU_10.2_8_128404843)



In the candidate regions that presented selection, ENSEMBL genes were identified through five chromosomes (Table 2). The regions with SSs were 15026769 to 103492964 of chromosome 3, 10553433 to 66661654 of chromosome 5, 134659633 to 134777072 of chromosome 6, 12300999 to 102777822 of chromosome 7, and 118251236 to 128953331 of chromosome 8. In the QTL alignment, 146 were associated, which were distributed in 7 chromosomes, located in the regions: 1456046 to 143758669 of chromosome 3, 844337 to 109562487 of chromosome 5, 25859176 to 146365886 of chromosome 6, 48748 to 134608551 of chromosome 7, 3470575 to 148491826 of chromosome 8, 5836383 to 209900460 of chromosome 13, and 342954 to 83197113 of chromosome 16. The identified QTL are grouped into behavior (time spent eating, coping behavior), conformation (ear position and ear area, number of vertebrae, leg and leg conformation), fatness (area, weight, percentage and distribution of fat, marbling, adipocyte diameter), immune capacity (level of the toll-like receptors 2 and 9, induced cell proliferation, C3C concentration, percentage of positive leukocytes, complement hemolytic activity, number of segmented neutrophils, white blood cell count, phagocytic activity), reproduction (uterine capacity, weight of the reproductive tract, number of nipples, age at puberty, length of gestation).

Table 2: Genes located in regions with selection signals

Gene name	ID	Function	Domain
ENSSSCG00000007733	GO:0005509	Calcium ion binding	Molecular function
GALNT17*	GO:0000043	Polypeptide N-acetylgalactosaminyl transferase	Molecular function
VIT*	GO:0000107	Vitrin	Biological processes
RAC2	GO:0007264	Small GTPase-mediated signal transduction	Biological processes
SSTR3	GO:0004994	Somatostatin receptor activity	Molecular function
C1QTNF6	GO:0005515	Protein binding	Molecular function
ENSSSCG00000029668 (IL2RB)	GO:0004896	Cytokine receptor activity	Molecular function
TMPRSS6	GO:0006508	Proteolysis	Biological processes
CRACR2A	GO:0003924	GTPase Activity	Molecular function
PARP11	GO:0003950	NAD + ADP-ribosyltransferase activity	Molecular function
IFI44L*	GO:0000107	Protein containing the TLDc domain	Biological processes
PTGFR	GO:0004958	Prostaglandin F receptor activity	Molecular function
NRXN3			
ATXN1	GO:0045892	Transcription downregulation, DNA template	Biological processes
MANBA	GO:0005975	Carbohydrate metabolic process	Biological processes
NFKB1	GO:0006357	Regulation of transcription by RNA polymerase II	Biological processes

The following describes 16 candidate genes identified in regions with SSs in the MHP. 1) ENSSSCG00000007733, it is considered a new gene involved in umbilical hernias(27). 2) VIT Vitrin, it is related to scrotal and umbilical hernias(28,29). 3) RAC2 C3 Botulinum toxin substrate, it is a GTPase that is expressed in hematopoietic cells with functions in leukocytes and neutrophils(30) and participates in the regulation of different cell cycle regulatory pathways, apoptosis, and immune response(31). 4) SSTR3, it is one of the five genes encoding somatotropin receptors and is expressed in the pituitary(32). 5) C1QTNF6, tumor necrosis factor-related protein 6, it controls subcutaneous and intramuscular fat deposition through the MAPK, p53, TNF, and adipokine signaling pathways(33). 6) TMPRSS6, type two transmembrane serine protease, matriptase – 2, proteolytic regulator of iron homeostasis[34]. 7) CRACR2A, calcium release activated channel regulator 2A; GTPase, it acts in the transmission of signals between the stimulation of the T cell receptor and the activation of the Ca^{2+}-NFAT and JNK-AP1 pathways[35]. 8) PARP11, member 11 of the ADP – poly ribosyltransferase (ADP-ribose) polymerase family, an important regulator of the antiviral efficacy of IFN-1[36]. 9) ENSSSCG00000029668 (IL2RB), interleukin-2 receptor, pleiotropic actions are essential for regulating the immune response and maintaining immune tolerance[37]. 10) PTGFR, prostaglandin F2α receptor[38]. 11) IFI44L, it is an interferon-specific inducible gene and can produce cellular GTP depletion, suppressing extracellular signal-regulated kinase signaling| and stopping the cell cycle[39]. 12) NRXN3 neurexin 3, candidate gene for susceptibility to neurodevelopmental disorders, mutations modify synaptic stability and function; it is synthesized in all excitatory and inhibitory neurons[40,41]. 13) ATXN1 ataxin-1, abnormal expression causes the neurodegenerative disease spinocerebellar ataxia type 1[42]. 14) CCSER1, it is a regulatory protein gene associated with economic traits such as growth, development, feed efficiency, and milk quality[43-46]. 15) MANBA beta-mannosidase, it plays important roles in regulating the immune system[47,48]. 16) NFKB1, nuclear factor of the kappa light polypeptide gene enhancer in B1 cells, regulators of immunity, cell proliferation, stress response, and apoptosis[49].

In the definition of a breed, genetic marks look for positive central regions immersed in artificial and natural selection in their environment[50,51]. SSs are derived from selection processes that have contributed to adaptation in different environments and production systems[52]. Unlike specialized breeds, in the MHP, selection has not been directed to parameters of economic interest but to conservation, adaptation, and evolution itself. Selection in conservation programs is developed with criteria associated with breed standards, aimed at the consolidation of specific traits and stabilization of the phenotype, with less pronounced changes in the frequency of related alleles[5]. SSs in native breeds are associated with domestication and the establishment of breed standards, not with parameters of economic interest given by artificial selection[53]. In relation to the length of the haplotype, it is related to natural selection (short regions) or artificial selection; however, there is no specific line that divides the type of selection, they may be influenced by each other and there may be overlapping regions in the genome[50]. Regarding native breeds, Muñoz *et al*[53] identified SSs in chromosomes in European breeds, with CG associated with reproduction, locomotor behavior, lipid metabolism, growth, and development; they also point out that chromosome 7 is associated with domestication processes and traits related to animal behavior. Chromosome 8 has been referenced with characteristics of growth, height, and conformation[52,54], as well as CG with response to immune diseases[55].

Chromosome 7 (Figure 2) presented a short and degraded haplotype, which can be related to adaptation processes; chromosome 8 showed a long and conserved haplotype, associated with a recent selection aimed at morphological parameters. In Laiwu pigs, a native breed recognized for its high intramuscular fat content[12,56], SSs have been reported, associating CG with characteristics of reproduction, development, growth, fatness, weight gain, feed intake, immune response, fat deposition, and litter size. Guo *et al*[50] identified CGs associated with disease resistance, reproductive traits, and meat quality as a result of the detection of SSs in the genome of a population of indigenous pigs from Anqing in China. Chen *et al*[57] reported QTL related to back fat thickness, meat color, pH value, fatty acid content, immune cells, parasitic immunity, and bacterial immunity. Wang *et al*[58] identified SSs in a population of Tunchang pigs, with CG related to adaptability, disease resistance, and lipid metabolism traits; with these characteristics, the researchers argue that the Tunchang breed is more related to native pigs than to specialized breeds. Quin *et al*[59] evaluated regions in the genome that underwent selection associated with CGs that regulate immunity and fat deposition in pigs native to Shandong, China. Gurgul *et al*[5] studied pig breeds in conservation programs in Poland, where they detected several SSs with CG associated with metabolic pathways, immune system response, and embryonic development. In Iberian and Casertana breeds, QTL and genome scans have identified regions and mutations related to morphological aspects, productive parameters, health, and meat and carcass characteristics[52,60]. SS have been identified for native pigs of Huainan and their cross with the Duroc breed, where QTLs were associated for intramuscular fat content in the native breed and for the cross, they were associated for triglyceride content, mummified pigs, hemoglobin, and loin muscle depth; the detection of SS is a viable tool for evaluating productive performance in the crossing of native pigs with specialized breeds[61], so genomic information plays an important role in the improvement of conservation programs[62].

It is concluded that the MHP underwent selection, and CG and QTL associated with immune system response, adaptation, behavior, obesity, embryonic implantation and development, meat quality due to intramuscular fat, growth, development, and feed efficiency were identified; they were also associated with morphological characteristics that can distinguish it from other breeds; it was also observed that undesirable candidate genes related to umbilical and scrotal hernias were indirectly selected.

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