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Genome-wide association study for heat stress resistance in Brown Swiss cattle in Yucatan, Mexico

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Additional information and declarations can be found on page 11

Abstract

Global climate change has made heat stress tolerance an important trait to be considered in breeding programs to improve the resistance of productive animals to unfavorable environmental conditions. The aim of this study was to know the association between single nucleotide polymorphism (SNP) markers and heat stress resistance through a genome-wide association study (GWAS). Where 95 Brown Swiss dairy cows have measured body temperatures, respiratory frequencies, and genotypes. Seven SNP were detected with a statistically significant effect ($P < 0.01$) on respiratory frequency under heat stress. The markers with the highest association are in the *Bos taurus* autosome 6 (BTA 6), e.g. the BovineHD0600010397 SNP located within the *FAM13A* gene, and the BovineHD0600012612 SNP located within the *PI4K2B* gene. The ARS-BFGL-NGS-102407 SNP that is located in BTA 4 is the SNP that presents the highest number of associations to genes. Most of the genes are involved in cellular processes that are present in the resistance of individuals to high and humid environmental temperatures. These results provide new insights into the genetics of heat stress tolerance in Brown Swiss cattle in Yucatan, Mexico.

Keywords: Heat stress; Genome-Wide Association; Brown Swiss; Respiratory frequencie; Global warming

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Study contribution

Global warming is a major problem that compromises the welfare of animals trying to maintain their homeostasis and continue their production to feed the more than 130 million people currently living in Mexico. For this reason, it is necessary to conduct research that indicates that there are populations of productive animals with genes that confer resistance to heat stress. This study demonstrated the existence of single nucleotide polymorphisms that are associated with genes whose expressions produce proteins that confer heat resistance to the animal. This study opens a very important line of research in Mexico to continue with studies in the Brown Swiss breed and to be able to generate reference populations in the medium term to implement genomic selection programs in this trait of economic interest.

Introduction

Climate change represents one of the major problems affecting livestock production worldwide. According to the Intergovernmental Panel on Climate Change (IPCC), the rate of global warming is 0.2 °C per decade, and it is expected that between 2030 and 2052 it could be as high as 1.5 °C. In this context, Mexico is the sixth country where a higher impact is expected in 2050 (4.2 °C).[1] This represents many challenges considering that it will make the task of feeding the 10 billion people who will make up the world population by 2050 more difficult, according to World Bank projections, and that its impact is already being felt in the fall in yields and extreme weather events affecting crops and livestock.[1]

The effects of high temperatures on the different physiological processes of living organisms have been extensively studied. The physiological adaptation to withstand high temperatures will depend on several biological factors that will help maintain the homeostasis of the individual.[2] In ruminants, heat stress (HS) occurs when an individual perceives a threat to its homeostasis.[2] HS not only affects the quantity and quality of milk produced but also has negative effects on fertility and feed intake. Some authors have reported that there are economic losses due to HS in geographic and climatic conditions similar to Mexico. Currently, due to the increase in temperatures, some countries have implemented genetic improvement programs in specialized dairy cattle that include tolerance to heat stress (THS) as a trait to be selected for.[3]

The main limitation in these populations is the determination of a phenotypic measure that allows the detection of tolerant animals at a low cost. One approach proposed by Misztal[4] is the use of existing dairy monitoring data (e.g. milk yield) together with data from weather stations (temperature, humidity) close to the farms to determine the slope of individual productive fall as a function of a heat load index. This measure has a low added cost but is a poor accurate measure of tolerance.[5] Some authors propose that rectal temperature should be the standard measure to objectively monitor the welfare of animals subjected to high heat load[6] and it has been used to assess the effect of the thermal environment on growth, lactation, and reproduction in dairy cattle.[7, 8]

However, with the current era of phenotyping, tools such as the thermographic camera have been used to facilitate the work in capturing the animal's body temperature, decreasing direct contact with the animal, and avoiding stress due to

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management.[9] The use of genotyping is a genetic tool that in the last 15 years has been used with great success because it favorably increases the precision of the genetic values of the animals for selection is the use of the animal's genotypes. The possibility of including genotypic data in the predictions of genetic values of individuals has opened up new possibilities for exploiting genetic resources in cattle populations.[10]

In this sense, genomics has influenced the genetic study of livestock, through methodologies such as the GWAS, which uses information from thousands of SNP distributed throughout the genome to estimate and quantify their effects to select and identify regions or *loci* involved in the expression of quantitative traits (QTL).[11] Studies such as that of Hernández-Cordero et al.[12] identified seven genes (*AVPR1A*, Furin, *IGFBP5*, *IGFBP6*, *PMCH*, *PRLR*, and *STAT5B*) associated with thermotolerance in Holstein dairy cattle in the Yaqui Valley, Sonora, Mexico. Other researchers reported six genes associated with milk production and its fat and protein content (*SFXN1*, *LOC781028*, *ANKRD31*, *LOC100296562*, *LOC107131388*, and *WDR41*) in a genome-wide association analysis conducted in Holstein cattle raised in the desert region of Mexicali, Baja California, Mexico.[13]

In the United States, Sigdel et al.[14], identified 10 genes associated with thermotolerance, since they participate in different cellular processes in response to HS, such as activation of HSP (*PEX16*, *HSF1*, *EEF1D*, and *VPS28*), reduction of oxidative stress (*CDKN1B* and *DUSP16*), modulation of the apoptosis process (*MAPK81P1*, *CREB3L1*), DNA maintenance (*TONSL*) and thermotolerance (*CRY2*). On the other hand, Dikmen et al.[15] found two genomic regions (BTA-24 and BTA-26) associated with the presence of thermotolerance genes in American Holstein cattle, which are related to rectal temperature and milk production, respectively. Correa-Calderón et al.[16] reported that, in the case of China, there is also evidence that their Holstein cattle carry SNP associated with thermotolerance genes such as *ATP1A1*, *HSP90AA1*, *HSF1*, *HSP70A1A*, and *HSPB1*.

The study of THS in the production systems of Mexico is essential in a competitive framework for the world supply of milk and meat, where an increase of 73 % and 58 %, respectively, have been predicted.[1] Therefore, this study proposes to identify single nucleotide polymorphisms (SNP) associated with physiological responses that indicate the presence or absence of heat stress in dairy cattle in Mexico to identify cattle tolerant to HS.

Materials and methods

Phenotypic data

The animals belonged to a ranch located in the community of port of Progreso, Merida, Yucatan. The average monthly temperatures and average relative humidity for the years 2019 and 2020 in the port of Progreso, Merida, Yucatan, are shown in the Figures S1A[1], S1B and S2.[17] Data from 95 cows with 2 038 milk production records up to 10 lactations (PL), 8 216 body temperatures (BT), and 10 022 respiratory frequencies (RF) were used. Animal temperatures were recorded with a FLIR E4 9 Hz thermographic camera and breaths per minute (BPM) were recorded on

1 The letter S in the references of Figures and Tables indicates that it is Supplementary Material

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the right side of each animal. Temperatures and respiratory frequencies were sampled twice a week, twice a day (once in the morning and once in the afternoon) from October to December 2019 and from January to March 2020. In the edition of each variable, extreme values at three standard deviations from the mean were removed and assigned as missing values.

Meteorological data

Environmental temperatures (ET) and environmental relative humidities (RH) were recorded in the milking parlor at the same time as the physiological information through a digital thermohygrometer. The temperature-humidity index (THI) per day of physiological records was calculated considering temperature (T) and relative humidity (RH) as follows:[18]

$$THI = (1.8 \times ET + 32) - (0.55 - 0.0055 \times RH) \times (1.8 \times ET - 26)$$

Extreme values at three standard deviations from the mean were eliminated and assigned as missing values. Table S1 shows the classification according to the THI for the farm where the cows' physiological measurements were obtained.

Genotypic data

Ninety-five cows were genotyped using the Illumina GGP Bov 100K chip. Genotypes were edited according to a control of call rate > 0.90, minor allele frequency (MAF) > 0.02, Hardy Weinberg equilibrium (HWE) $P > 0.001$, discard of markers with Mendelian errors, and GCScore > 0.25. A total of 69 848 SNP were used genome-wide. SNP positions were coordinated according to the ARS-UCD1.3 reference set.

Statistical model

A GWAS was performed to obtain the associations with possible genes involved in resistance to heat stress through SNP markers, measured through their respiratory frequency. A multiple linear regression mixed models was performed, with the following terms:

$$y_{ijkl} = \mu + \beta_1 r_i + \beta_2 t_j + \beta_3 g_k + u_l + e_{ijkl}$$

where y is the respiratory frequency; r is the temperature of the thermographic chamber; t is the THI; g is the SNP; β_1, β_2, β_3 are the coefficients of the fixed linear regressions for r, t, and g, while u is the random effect of the animal that was included to take into account the multiple measurements of each cow, and e is the associated error. The effect of each SNP was estimated and its significance value was adjusted by the false discovery rate (FDR) and then transformed to its negative logarithm base 10, and a Manhattan plot was performed to identify significant SNP ($P < 0.05$). Analyses were performed using R statistical software.[19]

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Table 1. Descriptive statistics for phenotypic traits

Trait	Mean	Min	Max	CV
Breaths per minute (bpm)	41 ±11	16	88	0.28
Body temperatures (°C)	37.5 ±0.8	27.9	40.1	0.02
Temperature-humidity index	73 ±5	61	82	0.07

Breaths per minute (bpm); Celsius degrees (°C)

Results and discussion

Descriptive statistics for the phenotypic characteristics involved in the statistical model are shown in Table 1. A mean for respiratory frequency of 41 ± 11 breaths per minute is observed, with a minimum value of 16 and a maximum of 88, with a coefficient of variation of 28 %. Concerning body temperature measured with the thermographic camera, the mean was 37.50 ± 0.84 °C, with a minimum value of 27.9 and a maximum of 40.1 with a coefficient of variation of 2 %. And the temperature-humidity index had an average of 73 ± 5, with a minimum value of 61 and a maximum of 82, with a coefficient of variation of 7 percent.

Figure 1 shows the genomic association and the significant associations between the markers and the respiratory frequency of the animal under heat stress. The regions with a clear signal of effect on the trait were in BTA 4, 6, 10, and 17. On chromosome 6 two spots are observed, the reason is that there are 3 SNP (BovineHD0600012612, ARS-BFGL-NGS-21182, and Hapmap41353-BTA-76120) with very short distances between them (44831889, 45112831, and 45935611 bp) that could be inherited together.

The effects of THI and body temperature were significant in the models. Likewise, the random effect of animals on average accounted for about 3.9 % of the total variation in the models for respiratory frequency. Seven significant SNP ($P < 0.05$) were detected to affect respiratory frequency under heat stress. The most significant SNP markers are found flanking the region between 35992596 and 45935611 bp in the BTA 6. The SNP located in BTA 4 is the one that presented an association with more genes. Also, BTA 10 and 17 have a highly significant effect on the trait.

Table 2 shows the regression coefficients for the independent variables THI and BT and the genotypes of each SNP. The results indicate a statistically significant ($P < 0.01$) linear relationship between THI and SNP indicating that respiratory frequency increases between 0.69 and 0.70 bpm for each unit change in THI.

Similarly, a statistically significant linear relationship ($P < 0.01$) was observed between BT and RF indicating that respiratory frequency increased between 3.48 and 3.59 bpm for each unit change in body temperature. A favorable association was detected between the SNP rs110968187 (ARS-BFGL-NGS-102407) with a decrease in the respiratory frequency of -2.23 and -4.37 bpm of the heterozygote and homozygote respectively (Figure 2). This SNP is in the 75602694 regions of chromosome 4, and the genes with which it can be associated are *TNS3*, *TRNAR-ACG*, *ADCY1*, *CAMK2B*, *ADAM22*, *COA1*, *HECW1*, *OGDH*, *NUDCD3*, *GLI3*, *FAM221A*, *OSBPL3*, *MPP6* and *IGFBP3* (Table 3). The *TNS3* (Tensin 3) gene is involved in mammary cell migration and has been reported as a candidate gene in tumor cell

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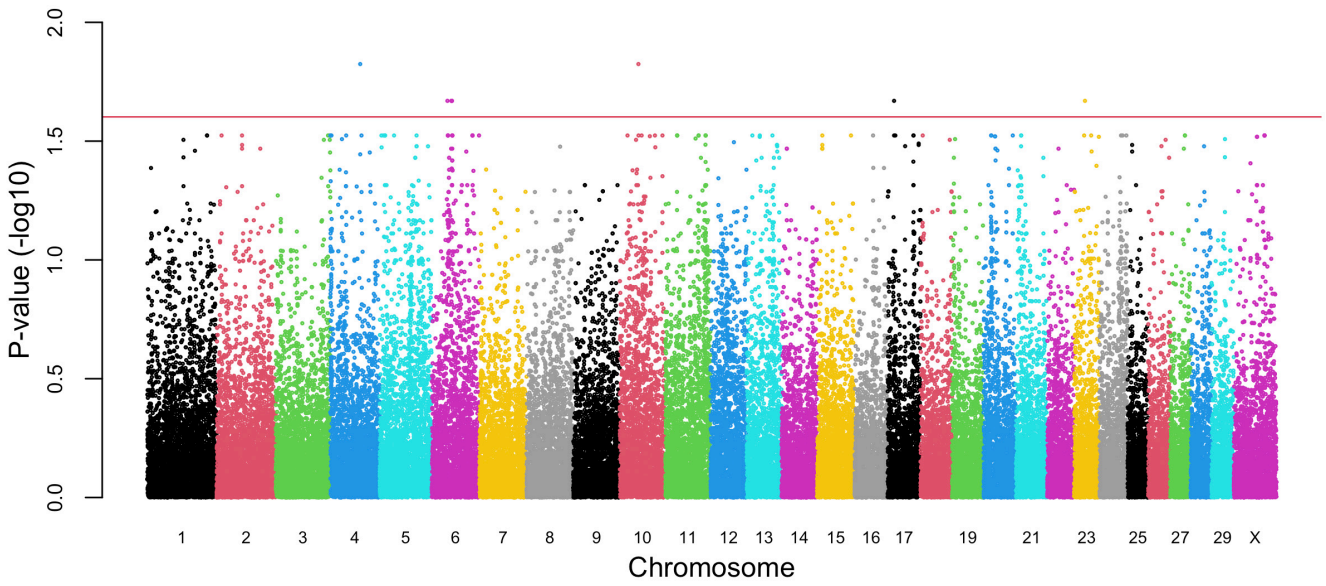

Figure 1. Manhattan plot showing the significance -log10(P-value) for SNP effects for respiration rate under heat stress in Brown Swiss cattle in Mexico.

Table 2. List of SNP molecular markers that were found to be significant in the genome-wide association study

SNP Name	SNP_ID	Coefficients		Genotype		
		THI	TC	AA	AB	BB
ARS-BFGL-NGS-102407	rs110968187	0.7**	3.49**	-103.31**	-2.23**	-4.37**
BovineHD0600010397	rs469925373	0.7**	3.55**	-109.67**	1.75**	5.04**
BovineHD0600012612	rs137814830	0.7**	3.50**	-101.92**	-2.45^{NS}	-5.80**
ARS-BFGL-NGS-21182	rs110652103	0.7**	3.50**	-107.72**	3.35**	5.80**
Hapmap41353-BTA-76120	rs41652054	0.7**	3.50**	-101.92**	-2.45 ^{NS}	-5.80**
BovineHD1000012735	rs43625771	0.7**	3.48**	-101.40**	-3.28**	-5.61**
BovineHD1700003830	rs132824650	0.69**	3.59**	-111.48**	2.28**	4.51**

** $P < 0.01$
NS = not significant ($P > 0.05$)

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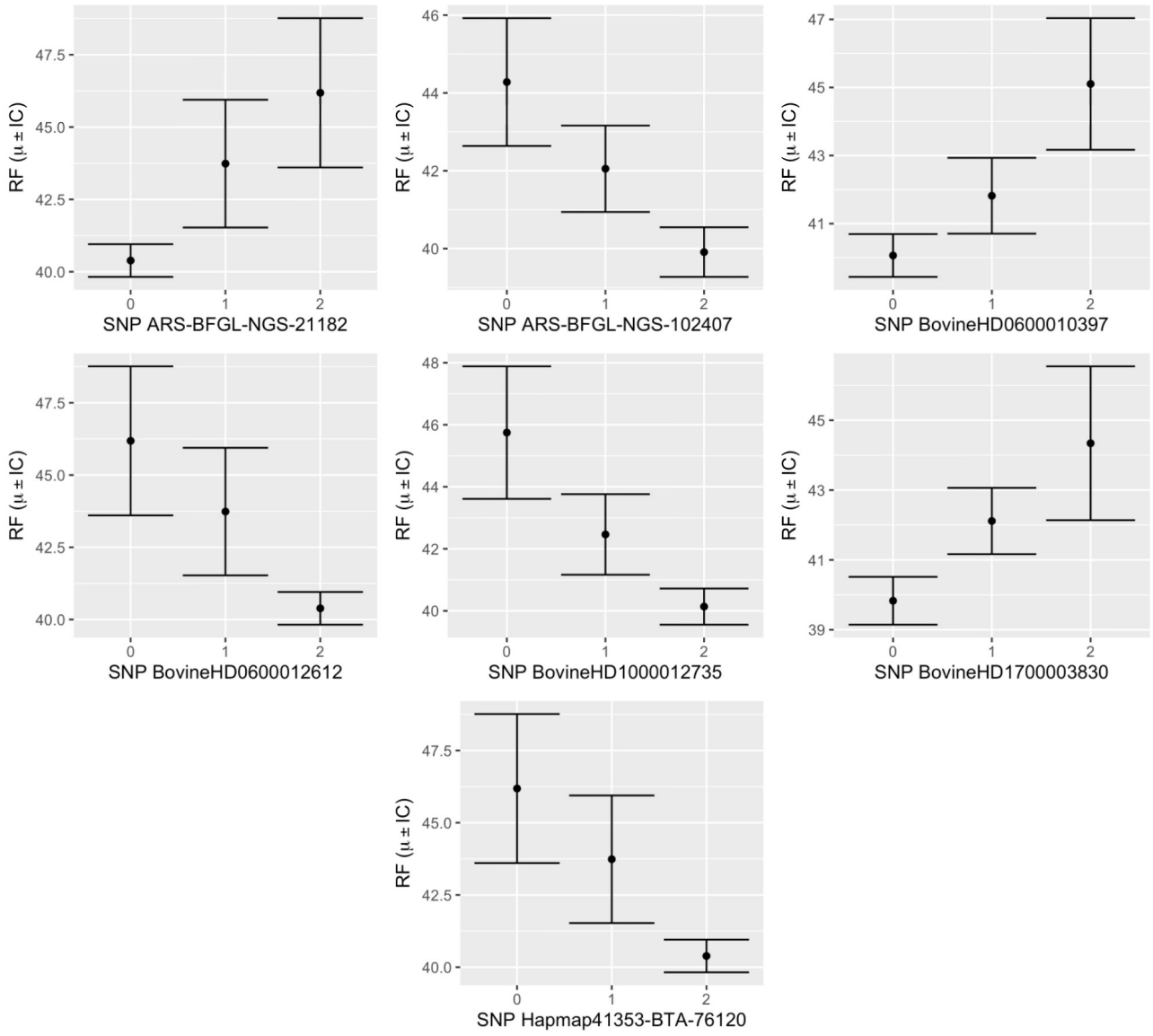

Figure 2. Distribution of the marginal means of the respiratory frequency (RF) in each genotype for each significant SNP.

lines,[20] the *TRNAR-ACG* gene is an arginine RNA transferase that functions as an ACG-anticodon producing mutations in this family of isogenic RNA transferases.[21] This gene was reported as a candidate gene responsible for genome transformation to generate tolerance to high temperatures in microorganisms such as yeasts.[21] The *ADCY1* gene is involved in the body condition index in zebu and synthetic breeds for adaptation to climates with high temperatures and was reported as a candidate gene.[22] The *FAM221A* gene reported as a candidate gene,[23] intervenes in the processes to maintain homeostasis in several biological systems such as immune, growth and development, cardiovascular, humoral, reproductive, skeletal, respiratory, ocular, hematopoietic and reproductive. The *IGFBP3* gene is involved in milk production under heat stress like other genes of the same family (*IGFBP5* and *IGFBP6*) reported in the heat-stressed Holstein breed in the Yaqui Valley, Sonora, Mexico.[12]

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Table 3. Genes to which the 7 significant SNP obtained from the GWAS study are associated with the trait respiratory frequency in Brown Swiss dairy cows at high temperatures and relative humidities

SNP_ID	Chr	Base pairs	Alleles	P-value	Gene associated to
rs110968187	4	75602694	G/A	4.29E-07	TNS3
					TRNAR-ACG
					ADCY1
					CAMK2B
					ADAM22
					COA1
					HECW1
					OGDH
					NUDCD3
					GLI3
					FAM221A
					OSBPL3
					MPP6
					IGFBP3
rs469925373	6	35992596	A/G	1.54 E-06	FAM13A
rs137814830	6	44831889	G/A	2.18E-06	PI4K2B
					ZCCHC4
					ANAPC4
rs110652103	6	45112831	A/T	2.18E-06	LOC112447058
					SLC34A2
					LOC112447057
					LOC112447059
					LOC112447218
					ANAPC4
rs41652054	6	45935611	G/A	2.18E-06	CCKAR
rs43625771	10	41722547	G/A	2.29E-07	MDGA2
rs132824650	17	13124955	A/G	2.45E-06	OTUD4

A = Adenine, G = Guanine, T = Thymine

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A favorable association was also observed between the SNP rs43625771 (BovineHD1000012735) with a decrease in the respiratory frequency of -3.28 and -5.61 of the heterozygote and homozygote, respectively (Figure 2). This SNP is located in the 41722547 region of chromosome 10, and the gene that can be associated with it is *MDGA2*, this gene encodes for the domain containing glycosylphosphatidylinositol 2 anchor involved in the regulation of presynapse assembly, the regulation of synaptic membrane adhesion and differentiation of motor neurons in the spinal cord, it also participates in the process of migration and pattern specification of neurons, activates GABAergic synapses and glutamatergic synapses; this gene was reported in a scientific study in Germany as a candidate gene in Holstein cattle under heat stress.[24]

For SNP rs469925373 (BovineHD0600010397), rs110652103 (ARS-BFGL-NGS-21182), and rs132824650 (BovineHD1700003830) associations with increased respiratory rate were observed; for the first SNP, it was 1.75 and 5.04 bpm, for the second of 3.35 and 5.80 bpm and the third of 2.28 and 4.51 bpm of the heterozygote and homozygote respectively (Figure 2). The first SNP (rs469925373) is located in the 35992596 region of chromosome 6, and the gene that can be associated with it is *FAM13A*, this gene encodes an active regulator in the H3K27ac region of the adipose nuclei increasing the distribution of body fat in the subcutaneous adipose tissue and affects the function of the adipocyte.

In a study[25] in Holstein cattle, it was reported that the FAM13A gene produces transcripts that are complementary to adjacent genes, which encode extracellular matrix proteins that contain essential sequences for interactions between integrins and receptors located in the BTA 6, within a quantitative trait locus (QTL) that affects milk protein production. The genes of this cluster are involved in the formation of tubuloalveolar structures in the mammary gland and renal function. In humans, the FAM13A gene was reported as a candidate gene responsible for insulin resistance disease that can predispose to the development of type 2 diabetes, cardiovascular diseases, and hyperglycemia.[26]

The second SNP (rs110652103) is located in region 45112831 and also found on chromosome 6, and the genes with which it can be associated are *LOC112447058*, *SLC34A2*, *LOC112447057*, *LOC112447059*, *LOC112447059*, *LOC112447218* and *ANAPC4* (Table 3). The *ANAPC4* gene participates in the anaphase promoter subunit 4 complex in cell division processes.[23] The *SLC34A2* gene encodes the phosphate ion co-transporter of the cell and in the transmembrane transport of sodium ions for the transport of inorganic phosphate, amino acids, and casein in cells, this gene was reported as a candidate gene that is expressed when mammary cells are under heat stress.[27] It was also reported to participate in meat quality and body composition in Nellore cattle.[28] The genes *LOC112447057*, *LOC112447058*, *LOC112447059*, and *LOC112447218* are not yet characterized. The third SNP (rs132824650) is located in region 13124955 on chromosome 17 and the gene with which it can be associated is *OTUD4* which codes for the enzyme OTU deubiquitinator 4 and participates through both catalytically dependent and independent mechanisms to regulate the activity of TGFβ (transforming growth factor-β), this pathway is crucial for embryonic development, as well as for the maintenance of tissue homeostasis in adult tissues.[23]

SNP rs137814830 (BovineHD0600012612) and rs41652054 (Hapmap41353-BTA-76120) presented a favorable and significant association with the

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homozygous genotype and favorable but not significant with the heterozygous genotype (-5.8 and -2.45) respectively. Both are located on chromosome 6; the first SNP is at a location of 44831889 bp and the second at 45935611 bp. The genes to which they are associated are shown in Table 2; the *PI4K2B* gene is reported as a candidate gene, it codes for a cytosolic protein and contributes to PI4 kinase activity along with other proteins that together participate in the early activation of T cells.[29] The *ZCCHC4* gene is also known as the *HSPC052* gene, which is part of the family of genes that express proteins to counteract the effects of heat stress, participating in the adaptation of the animal to climates with very high temperatures.[30] The *CCKAR* gene participates in the calcium signaling pathway and was reported as a candidate gene associated with growth characteristics and carcass quality in Hanwoo cattle.[31]

Conclusions

In the GWAS study, a total of 7 SNP associated with changes in respiratory rate were identified; for the 7 SNP, AA homozygotes had a lower respiratory rate compared to heterozygotes or homozygotes, this indicates that animals presenting the AA genotypes present resistance to heat stress, AG or AT heterozygotes have an intermediate response to heat, while GG or TT genotypes increase respiratory rate, indicating that animals with these genotypes will be susceptible to heat stress. For each of these SNP, several associations were found with genes related to protein production, maintenance of body condition and cellular metabolism, and physiological processes involved in adaptation to climates with high temperatures and environmental relative humidities. These results provide new insights into the genetics of heat stress tolerance in Brown Swiss dairy cattle.

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Data availability

If access to the data is desired, please contact the corresponding authors.

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Conflicts of interest

Hugo Oswaldo Toledo-Alvarado is member of the editorial board of Veterinaria México OA. Following the current journal's policies in this regard, he only participated as author during the editorial process of this submission. Moreover, all authors agreed to publish the peer review process along with the article.

Author contributions

Conceptualization: NSS, TAH, BVJ, MMJ, CMN
Data curation: NSS, TAH
Formal analysis: NSS, TAH
Acquisition of funds: BVJ, UAR
Research: NSS, TAH, MMJ, OGP
Methodology: NSS, TAH
Validation: TAH
Drafting-original draft: NSS
Drafting-revision and editing: BVJ, CMN, MMJ, OGP, UAR, TAH

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