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Selection signatures in candidate genes and QTL for reproductive traits in Nellore heifers

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ABSTRACT

The identification of selection signature genes may help to detect genomic regions that underwent artificial selection and contributed to phenotypic diversity. The aim of this study, therefore, was to detect selection signatures in candidate genes and quantitative trait locus (QTL) for reproductive traits in a Nellore population being selected for sexual precocity. A total of 2035 Nellore heifers, sourced from breeding programs focused on sexual precocity, were used. Candidate genes and some specific QTL related to reproductive traits were chosen based on published literature and Animal QTL databases, respectively, for investigation whether these regions were affected by selection. Selection signature DNA sequences were detected in the selected regions using the extended haplotype homozygosity (EHH) and relative extended haplotype homozygosity (REHH) methods. From 22,241 single nucleotide polymorphisms (SNPs) located in the candidate genes and QTL, 17,312 SNPs generated 2756 haplotype blocks. A total of 7518 EHH tests were analyzed using haplotypes with a frequency of more than 25%, for which there were 39 tests that were significant for REHH ($P < 0.01$). Selection signature DNA sequences were detected that contained several QTLs for important reproductive traits in cattle, suggesting that reproductive traits may have been affected by selection for sexual precocity in this population. Forty-six genes were located in the selection signature regions, whereas 24 genes participated in important biological processes or pathways that may underlie sexual precocity. These results indicate there are possible molecular mechanisms related to sexual precocity in the Nellore breed.

1. Introduction

Reproductive traits have high economic importance in beef cattle production systems, especially in tropical environments (Brumatti et al., 2011). Thus, selection for sexual precocity and reproductive efficiency has been widely used in Nellore cattle breeding programs in Brazil (Lôbo et al., 2008). Artificial selection alters the frequency of genetic variants that affect the selected traits, and results in patterns of polymorphisms in strong linkage disequilibrium (LD), referred to as selection signatures, which

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become prevalent in the population (Sabeti et al., 2002; Innan and Kim, 2008; Oleksyk et al., 2010).

Selection signatures can be detected using the extended haplotype homozygosity (EHH) method (Sabeti et al., 2002). This method is based on the rapid increase of a mutation frequency in the population under positive selection that results in regions with an unusually strong and long-range LD with high haplotype allele frequency (Bomba et al., 2015). There can be large amounts of EHH that also occur due to a low recombination rate in specific genomic regions (Qanbari et al., 2010). To account for this, Sabeti et al. (2002) developed the relative extended haplotype homozygosity (REHH) method, which corrects EHH for the variability in recombination rates.

The identification of selection signatures may help to detect genomic regions that underwent artificial selection and contribute to phenotypic diversity (Utsunomiya et al., 2013; Qanbari et al., 2011). Furthermore, it is important to identify selection signatures that harbor quantitative trait locus (QTL) as an indicator that there is a relationship between selection and the effects of the variants on the phenotype (Barendse et al., 2009). The aim of this study, therefore, was to detect selection signatures in candidate genes and QTL for reproductive traits in a Nellore cattle population in which there is selection for sexual precocity. In addition, there was a focus on identifying genes that contain the selection signature regions to verify whether biological processes are related to sexual precocity.

2. Materials and methods

2.1. Animals

This study was approved by the Ethics Committee on Animal Experimentation (CEUA) of the School of Agricultural and Veterinary Sciences (FCAV/UNESP) Jaboticabal, São Paulo, Brazil (protocol nº17958/15).

The 2035 Nellore heifers used in this study were born between 2007 and 2009, belonged to Agropecuária Jacarezinho Ltda. (AJ) with participation in the DeltaGen breeding program occurring. Animals of the Nellore breed have been selected for production and reproductive traits since its introduction in Brazil about 60 years ago (Oliveira et al., 2002). Starting about 40 years ago, the selection for these traits was intensified upon the development of breeding programs in Brazil (Ferraz and de Felício, 2010), whereas in the AJ herd there has been use of the age at first calving trait as selection criteria to select sexually precocious heifers since 1993. In the AJ herd, there has been two breeding seasons. The early breeding season lasts approximately 60 days (February to April), during which all heifers are exposed to bulls at an early age, between 14 and 16 months, regardless of body weight and condition. Artificial insemination, controlled breeding, or multiple-sire breeding with a bull:cow ratio of 1:30 are used. Pregnancy is confirmed about 60 days after the end of the anticipated breeding season, wherein heifers that did not conceive during their first breeding season are exposed again to bulls at 2 years of age. Failure to conceive before 2 years of age, inability to conceive in any subsequent year, and less than desirable progeny performance are considered criteria for the culling of heifers.

2.2. QTL and candidate genes

Candidate genes and some specific QTL related to reproductive traits were chosen based on published literature and Animal QTL database (Hu et al., 2013), respectively, for investigation whether these regions of DNA were affected by selection. All information about the selected candidate genes and QTL are available in Supplementary Tables 1 and 2, respectively.

2.3. Genotyping and quality control

The DNA was extracted from hair follicles collected from the tail switch using the phenol/chloroform/isoamyl alcohol method (Sambrook and Fristch, 1989). Genotyping was performed using the Illumina BovineHD BeadChip, which that contains 777,962 single nucleotide polymorphisms (SNPs). Quality control of genotypes was assessed using the GenomeStudio software version 2011.1 (Illumina Inc. EUA) to remove samples with a call rate < 0.90. Only SNPs mapped on candidate genes and QTL, with a call rate > 0.90, minor allele frequencies > 0.05, and not in highly significant deviation from the Hardy-Weinberg equilibrium ($P > 10^{-5}$) were considered for further analyses. A total of 22,241 SNPs from the selected regions remained after applying the filtering criteria for further analysis (Table 1).

2.4. Haplotype and LD analysis

The fastPHASE software was used to reconstruct the haplotypes and missing genotype estimation (Scheet and Stephens, 2006). The LD estimation was performed using Haploview software (Barrett et al., 2005) based on estimated r^2 (Hill and Robertson, 1968). The SNPs that were not part of any haplotype were considered isolated markers. A total of 2756 haplotype blocks were generated with an average size of 27.57 ± 29.08 kb, spanning 70.05 Mb.

2.5. REHH analysis

The Sweep v.1.1 software was used to search for core regions in the selected regions (Sabeti et al., 2002). Sweep implements an algorithm that defines a pair of SNPs to have a large amount of LD if the upper 95% confidence bound D' is between 0.7 and 0.98, as suggested by Gabriel et al. (2002). Core regions with at least three SNPs and not more than 20 SNPs were selected. The EHH and REHH tests were applied to the two most frequent haplotypes on each core region. The EHH of core haplotype t is calculated as:

Table 1
Description of single nucleotide polymorphisms (SNPs) and haplotype blocks (HB) distributed across the selected regions.

BTA	N_SNP	MDB_SNPs (kb)	N_HB	MHBL (kb)	HBCL (kb)	Max_HBL (kb)	N_SNPs in HB	Max SNPs in HB
1	1664	95.16	213	24.17	5148.38	128.60	1241	20
2	449	305.26	62	24.73	1533.36	178.52	311	12
3	520	233.52	51	38.58	1967.82	157.37	447	20
4	291	415.22	32	25.14	804.56	176.62	188	20
5	2518	48.13	308	28.47	8767.77	189.28	2074	20
6	1314	90.91	169	21.46	3627.09	83.80	1087	20
7	1432	78.66	182	18.07	3289.26	97.81	1071	20
8	361	314.07	50	20.23	991.42	87.38	247	12
9	843	125.40	110	24.36	2679.88	160.34	719	20
10	725	143.88	80	37.33	2986.57	156.72	628	20
11	760	141.20	110	17.97	1976.31	84.64	557	20
12	316	288.48	33	30.64	1011.12	122.58	242	20
13	1893	44.50	233	25.04	5833.59	154.22	1438	20
14	2342	36.14	290	29.70	8612.53	1324.36	1875	20
15	269	317.06	30	39.85	1195.61	222.91	207	20
16	441	185.31	45	32.18	1448.09	114.44	340	19
17	419	179.38	62	12.54	777.44	47.73	297	18
18	594	111.11	61	39.24	2393.93	208.24	502	20
19	1181	54.24	153	22.03	3370.75	120.29	904	20
20	1011	71.26	134	20.56	2755.00	240.63	705	20
21	926	77.32	104	26.67	2773.88	118.22	687	20
23	237	221.65	18	68.39	1231.07	177.25	229	20
24	799	78.49	97	24.83	2408.87	126.97	630	20
27	223	203.63	31	16.56	513.36	40.44	165	10
29	713	72.24	98	20.50	2009.17	94.71	521	16
Total	22,241		2,756		70,106.81		17,312	
Mean		157.29		27.57		184.56		18.68

BTA = *Bos taurus* autosome; N_SNP = number of SNPs in the regions; MDB_SNPs = Mean distance between SNPs; N_HB = number of haplotype blocks; MHBL = Mean haplotype block length; HBCL = haplotype blocks coverage length; Max_HBL = Maximum haplotype blocks length; N_SNPs in HB = number of SNPs in haplotype blocks; Max SNPs in CR = maximum number of SNPs in haplotype blocks.

$EHH_t = \sum_{i=1}^{s} \binom{e_{ti}}{2} / \binom{C_t}{2}$; where s is the number of unique extended haplotypes, e_{ti} is the number of samples of a particular extended haplotype i and C_t is the number of samples of a particular core haplotype t.

To correct EHH for the variability in recombination rates, REHH was performed by comparing the EHH of the tested core haplotype to the EHH of other core haplotypes at the same locus (Sabeti et al., 2002). Therefore, REHH was calculated as follows: $REHH_t = EHH_t/\overline{EHH}$; where: $\overline{EHH}$ is the relative homozygosity on the chromosome, defined as the decay of EHH on all other core haplotypes combined. The $\overline{EHH}$ was calculated as: $\overline{EHH} = \sum_{j=1,j\neq t}^{n} \left[\sum_{i=1}^{s} \binom{e_i}{2} \right] / \sum_{i=1,j\neq t}^{n} \binom{c_i}{2}$, where n is the number of different core haplotypes.

For the application of the REHH test, a 250 kb window was used for both sides of the core haplotypes, due to the lesser LD observed in the zebu breeds compared to the taurine breeds (Espigolan et al., 2013; Somavilla et al., 2014). The haplotypes were ordered into ten bins according to their frequency and compared to the REHH for each common haplotype with the same frequency at a locus to determine the significance of the REHH tests. Furthermore, the REHH values were **log**-transformed to achieve normality. Significant core haplotypes were those that achieved significance levels of 0.01 with a frequency greater than 0.25 (Qanbari et al., 2010; Glick et al., 2012; Fan et al., 2014).

2.6. Annotation of the genes harboring selection signatures

Genomic regions with significant REHH values ($P < 0.01$) were extended by 30 kb on both sides (Mokry et al., 2014) to scan for genes related to sexual precocity. The amplitude of the window was shorter than that used for *Bos taurus* breeds (Qanbari et al., 2010; Fan et al., 2014; Bomba et al., 2015) due to the lesser extent of LD in Nellore cattle (Espigolan et al., 2013). Genes containing the significant selection signatures were identified using the NCBI Map Viewer tool based on the *Bos taurus* UMD3.1 reference assembly. The Gene Ontology (GO) and biological pathways annotations of the genes were retrieved using the *biomaRt* package (Durinck et al., 2009) and Reactome Pathway Knowledgebase (Fabregat et al., 2018), respectively.

3. Results and discussion

To investigate whether genomic regions associated with reproduction traits were affected by selection, selection signatures were searched for in the genome of Nellore heifers in which there was selection for early pregnancy. The identification of these regions when there is artificial selection practiced may provide for searching for regions or groups of genes that control reproductive traits

Table 2
Selection signature regions identified by extended haplotype homozygosity (EHH) and relative extended haplotype homozygosity (REHH) methodologies based on quantitative trait locus (QTL) and genes previously associated with reproductive traits.

BTA	EHH tests[1]	Sig tests[2]	Position (bp)	-Log_{10}(*P*-value REHH)[3]
1	568	3	38,864,433-38,930,065	2.15
			39,529,880-39,598,604	2.73
			44,242,642-44,346,061	2.47
2	192	2	64,828,631-64,902,508	2.01
			71,510,203-71,602,623	2.10
3	146	0	–	–
4	93	1	50,381,692-50,455,566	2.28
5	853	3	23,788,503-23,881,776	2.03
			28,552,221-28,629,665	2.16
			36,285,097-36,350,258	2.31
6	436	1	30,992,498-31,065,010	2.00
7	498	1	3,011,684-3,079,449	3.00
8	142	1	14,346,229-14,419,707	2.12
9	324	2	40,419,634-40,503,624	2.29
			50,658,167-50,725,784	2.09
10	229	0	–	–
11	294	2	37,228,780-37,291,133	2.37
			38,641,878-38,710,691	2.44
12	83	0	–	–
13	667	8	24,020,076-24,083,587	2.14
			41,115,351-41,178,728	2.27
			41,125,311-41,202,232	2.36
			41,148,514-41,211,985	2.37
			42,478,765-42,543,252	2.14
			42,613,940-42,716,842	2.11
			48,362,628-48,429,346	2.89
			48,617,062-48,688,022	2.06
14	821	2	4,751,237-4,817,006	2.89
			28,229,914-28,328,533	2.06
15	90	0	–	–
16	104	1	23,629,461-23,694,440	2.39
17	172	0	–	–
18	164	0	–	–
19	433	0	–	–
20	330	5	6,676,574-6,758,626	2.57
			16,216,130-16,312,341	2.21
			16,350,212-16,415,350	2.53
			16,415,092-16,483,764	2.01
			16,434,388-16,517,921	3.23
21	258	2	5,189,423-5,264,966	2.26
			6,586,616-6,664,038	2.51
23	38	0	–	–
24	249	3	16,341,917-16,439,807	2.02
			16,525,223-16,594,212	2.54
			16,973,152-17,052,179	2.04
27	64	0	–	–
29	270	2	27,621,242-27,708,039	2.16
			27,751,352-27,861,891	2.50
Total	7,518	39		

BTA = *Bos taurus* autosome; [1]Number of EHH tests with frequency more than 0.25; [2]Number of significant EHH tests at 0.01; [3]Values more than 2 and 3 are significant at 0.01 and 0.001, respectively.

(Somavilla et al., 2014).

Haplotypes with frequencies less than 25% were removed from the analysis of the remaining 7,518 EHH tests, whereas 39 were significant for EHH ($P < 0.01$) and REHH ($P < 0.01$) analysis (Table 2). These findings enabled the identification of potential genomic regions with recent selection signatures that may contain genes that underlie sexual precocity in Nellore cattle. Barendse et al. (2009) reported putative selection signatures near those that were detected in the present study in BTA 2, 11 and 16 in beef cattle. Selection signatures in BTA 2 at 71 Mb were also reported by Qanbari et al. (2011) in a Brahman cattle population. Somavilla et al. (2014) detected selection signatures in BTA 13 in the same region identified in the present study.

3.1. Candidate regions to harbor selection signatures

Selection signatures were not detected in the candidate gene regions that were analyzed, indicating that the selection applied to the population for sexual precocity evaluated in the present study did not affect these genes. This result could be because these genes

are controlled by natural selection or genetic drift processes based on the breed pedigree structure or are controlled by balanced selection processes (Porto-Neto et al., 2013).

The significant selection signatures ($P < 0.01$) detected in the present study contain several QTLs for important reproductive traits in cattle, including non-return-to-estrus rate (QTLs 5660, 10293, and 3573), conception rate (QTLs 3439, 4684, and 11544), pregnancy rate (QTLs 18822, and 18810), calving interval (QTL 18812), inseminations per conception (QTLs 35655, and 18813), age at puberty (QTLs 1379, 6201, 6099, 6161, 18818, 20683, 21138, 21148, 21144, 21145, and 21147), fertility index (QTLs 14720, 14761, 14770, 14772, and 14787), ovulation rate (QTLs 6026, 6027, 6028, and 10572), and early embryonic survival (QTLs 14808, and 14742), suggesting that reproductive traits may have been affected by selection for sexual precocity in the population of Nellore cattle used in the present study. According to Barendse et al. (2009), QTL and selection signatures in the same location indicate a precise relationship between the selection for some aspect of the phenotype and the effects of variation at the locus.

3.2. Genes containing selection signatures

Genes ($n = 46$) are located in the selection signature regions, with 24 of these gene products modulating important biological processes or pathways (Table 3). Among these, five gene products (*TBC1D23*, *NIT2*, *CELA1*, *BMPR1B,* and *HEXB*) there is modulation of the immune system pathway and inflammatory response process; and the *SPTBN1* gene product is involved in the MAPK signaling pathway. Inflammations occur during many normal reproductive processes; however, initiation and maintenance of inflammatory processes are important components of many reproductive tract diseases (Chen et al., 2017). Damaged tissues locally release inflammatory interleukins, growth factors, cytokines, and prostaglandins, which activate signaling pathways such as the MAPK pathway and recruit immune cells to the site of injury (Park et al., 2015; Chen et al., 2017). Banos et al. (2013) reported that there was a correlation between immune traits and reproductive traits in dairy cattle. Several beneficial associations between immune response and reproductive traits, including calving ease and number of services to conception, have been reported by Mallard et al. (2015).

The *TMEM117, BMPR1B* and *WNT9A* gene products are involved in the apoptosis process, which has fundamental importance in morphogenesis and oogenesis during embryonic development (Cui et al., 2011; Meresman, 2011). Results of several studies indicate there is an association between the apoptosis process and the death of oocytes and granulosa cells, suggesting that apoptosis is involved in the induction of follicular atresia (Tilly, 2001; Janowski et al., 2012). In cattle, it was reported that an apoptosis rate of 5%–30% in the granulosa cell layer affects the development of oocytes (Feng et al., 2007). Furthermore, the *BMPR1B* protein functions in ovarian cumulus expansion and the ovulation cycle, and was associated with ovulation rate in *Bos taurus* (Marchitelli and Nardone, 2015).

Gene products involved in the metabolism of lipids, such as *DBI, PIP4K2A,* and *HEXB,* also contain selection signatures. These lipids include cholesterol, phospholipids, and triacylglycerols, which provide energy and are also essential components in a variety of endocrine, cell signaling pathways, and contribute to the control of energy homeostasis (Mattos et al., 2000; Vernon, 2005; Wathes et al., 2007). According to Wathes et al. (2012), postpartum energy deficits result in activation of several metabolic signaling pathways that cause damage to oocytes and the endometrium, which contribute to a reduction in cow fertility. Furthermore, it was reported that SNPs in genes involved in lipid metabolism are associated with fertility in cattle. Li et al. (2009) reported that the *DBI* gene product modulates preovulatory regulation in response to the luteinizing hormone in cattle.

The gene products *CELA1*, *WNT3A, WNT9A* and *FERMT1* participate in the Wnt signaling pathway, which may affect the regulation of embryonic development (Tribulo et al., 2017). The Wnt signaling pathway modulates the regulation of granulosa cells and may inhibit the development of cattle embryos (Hernandez et al., 2009). Killeen et al. (2014) identified the *CELA1* gene in an endometrial gene expression analysis study of heifers with relatively greater and lesser fertility rates. Furthermore, from this study there was verification that *CELA1* gene expression occurred in a network of genetic expression associated with embryonic development. The genes *WNT3A* and *WNT9A* have functions *in utero* in embryonic development and embryonic forelimb morphogenesis, respectively.

The *MGC133636*, *CST8*, *CST9* and *CST11* gene products modulate biological processes of the negative regulation of endopeptidase activities, tissue inflammation and hormone processing, reflecting essential mechanisms of embryo implantation (Baston-Buest et al., 2010). In female mice, CST genes were expressed in the ovary, with their mRNA detected in the corpus luteum and granulosa cells of primary, secondary and mature follicles (Hsia and Cornwall, 2003).

Genes involved in the metabolism of proteins (*GFM2, GALNT6*, *TOMM70A,* and *ADAMTS17*), mRNA splicing (*CDC40*), and the regulation of intracellular pH (*SLC4A8*) may be involved in embryogenesis because the regulation of these genes is affected by many cellular processes. As reported by Killeen et al. (2014), the *GALNT6* gene was the most abundantly expressed gene in heifers with a relatively lesser fertility which may have consequences for embryo survival. Peddinti et al. (2010) reported that the *TOMM70A* product was involved in a biological network in the cumulus cell proteome of cattle.

The products of genes *LNP1, NCKAP5, C2H2orf76, METTL24, EML6* and *CCDC85A* did not have functions in any biological processes or pathways. The *CCDC85A* gene is expressed in the human endometrium (Brueggmann et al., 2014) and is located near the FSHR (follicle-stimulating hormone receptor) gene in cattle, which has been associated with age at puberty (Fortes et al., 2010). The expression of the *NCKAP5* gene was associated with feed efficiency traits (Serão et al., 2013), which are directly correlated to reproduction in cattle (Gunn et al., 2014). The expression of the *METTL24* gene has been associated with backfat thickness (Silva et al., 2017), which has been negatively genetically correlated with age at first calving in Nellore cattle (Caetano et al., 2013).

Selection signatures in BTA 29 indicate there is the presence of multiple genes and pseudo genes that are part of the olfactory receptor family (*LOC513062*, *LOC514864*, *LOC781383*, *OR8G2*, *LOC781319*, *LOC512722*, *LOC787694*, *LOC510984*, *LOC787625*,

Table 3
Genes located within or near the significant selection signature regions and their biological process and pathways.

Gene	BTA	Position (pb)	Biological process and pathways
TBC1D23	1	44,199,166-44,255,977	Regulation of inflammatory response (GO:0050727) Positive regulation of interleukin-6 production (GO:0032755)
NIT2	1	44,261,477-44,281,308	Immune System (R-BTA-168256) Innate Immune System (R-BTA-168249)
TOMM70A	1	44,292,838-44,332,178	Metabolism of proteins (R-BTA-392499)
LNP1	1	44,261,441-44,281,386	–
NCKAP5	2	64,102,656-65,214,068	–
C2H2orf76		71,473,526-71,561,177	–
DBI	2	71,561,192-71,566,372	Metabolism of lipids (R-BTA-556833)
LOC781951	4	50,369,381-50,383,710	–
GALNT6	5	28,543,995-28,615,499	Metabolism of proteins (R-BTA-392499)
CELA1	5	28,615,582-28,637,018	Inflammatory response (GO:0006954) Post-embryonic development (GO:0009791) Wnt signaling pathway (GO:0016055) Positive regulation of transcription (GO:0045944)
TMEM117	5	36,197,271-36,316,933	Intrinsic apoptotic signaling pathway in response to endoplasmic reticulum stress (GO:0070059)
SLC4A8	5	28,468,245-28,576,109	Regulation of intracellular pH (GO:0051453)
BMPR1B	6	30,797,077-31,322,263	Ovarian cumulus expansion (GO:0001550) Inflammatory response (GO:0006954) Ovulation cycle (GO:0042698) Positive regulation of transcription (GO:0045944) Positive regulation of extrinsic apoptotic signaling pathway via death domain receptors (GO:1902043) Cellular response to growth factor stimulus (GO:0071363)
WNT3A	7	2,948,313-3,017,653	Wnt signaling pathway (GO:0016055) In utero embryonic development (GO:0001701) Positive regulation of transcription (GO:0045944)
WNT9A	7	3,070,478-3,077,105	Wnt signaling pathway (GO:0016055) Embryonic forelimb morphogenesis (GO:0035115) Negative regulation of cysteine-type endopeptidase activity involved in apoptotic process (GO:0043154) Positive regulation of cell differentiation (GO:0045597)
CDC40	9	40,471,774-40,520,275	mRNA splicing, via spliceosome (GO:0000398)
METTL24	9	40,335,194-40,462,569	–
EML6	11	37,289,720-37,575,519	–
SPTBN1	11	37,028,024-37,241,384	MAPK family signaling cascades (R-BTA-5683057)
CCDC85A	11	38,706,388-38,930,062	–
PIP4K2A	13	23,899,335-24,086,139	Metabolism of lipids (R-BTA-556833)
LOC614124	13	41,140,057-41,141,499	–
MGC133636	13	42,481,841-42,485,869	Negative regulation of endopeptidase activity (GO:0010951)
LOC617402	13	42,488,775-42,493,106	–
CST8	13	42,500,560-42,508,896	Negative regulation of endopeptidase activity (GO:0010951)
LOC531692	13	42,520,281-42,529,176	–
LOC781567	13	42,533,830-42,536,605	–
CST9L	13	42,540,766-42,543,484	Negative regulation of endopeptidase activity (GO:0010951)
CST11	13	42,472,819-42,475,468	Negative regulation of endopeptidase activity (GO:0010951)
FERMT1	13	48,617,012-48,677,728	Negative regulation of endopeptidase activity (GO:0010951)
GFM2	20	6,669,159-6,740,437	Metabolism of proteins (R-BTA-392499)
HEXB	20	6,721,327-6,753,670	Metabolism of lipids (R-BTA-556833) Immune System (R-BTA-168256)
GABRG3	21	4,534,950-5,336,913	Transmission across Chemical Synapses (R-BTA-112315)
ADAMTS17	21	6,514,303-6,926,926	Metabolism of proteins (R-BTA-392499) Proteolysis (GO:0006508)
LOC513062	29	27,855,446-27,856,369	–
LOC514864	29	27,845,519-27,846,454	–
LOC781383	29	27,837,610-27,838,499	–
OR8G2	29	27,330,800-27,331,735	–
LOC781319	29	27,622,831-27,629,154	–
LOC512722	29	27,656,041-27,656,977	–
LOC787694	29	27,820,502-27,821,434	–
LOC510984	29	27,786,854-27,787,786	–
OR8D2	29	27,693,146-27,694,087	G-protein coupled receptor activity (GO:0004930) Signal transduction (GO:0007165) Sensory perception of smell (GO:0007608) Detection of chemical stimulus involved in sensory perception of smell (GO:005091)
LOC787625	29	27,770,678-27,771,604	–
LOC782191	29	27,750,649-27,751,581	–
LOC781359	29	27,615,864-27,618,144	–

BTA = *Bos taurus* autosome.

LOC782191, *LOC781359,* and *OR8D2*). Diedrichs et al. (2012) observed the expression of several olfactory receptor-encoding genes in human oocytes and suggested that these genes are involved in the development of female germ cells.

4. Conclusions

Genomic regions that are potentially linked to recent selection were identified in QTL regions for reproductive traits in Nellore heifers. The population studied was selected for sexual precocity, thus, results indicate there is homozygosity in these regions of the genome that are consequence of artificial selection. The selection signature regions contain several genes that have functions in relevant biological processes and pathways that may underlie sexual precocity. The investigation of these molecular mechanisms may elucidate which physiological functions were changed as a result of selection for sexual precocity and may contribute to the future improvement of reproductive traits in the Nellore breed.

Conflicts of interest

The authors have no conflict of interest to declare.

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Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:https://doi.org/10.1016/j.anireprosci.2019.06.004.

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