Journal of Animal Breeding and Genomics
pISSN:1226-5543 eISSN:2586-4297

JABG. 2018 September, 2(3): 151-162
https://doi.org/10.12972/jabng.20180030

Research Article
OPEN ACCESS

Revealing of Selection Signatures Underlying Adaptive and Production Traits in Hanwoo and Ethiopian Cattle Breeds

Zewdu Edea[1], Hailu Dadi[2], Tadelle Dessie[3], and Kwan-Suk Kim[1]*

[1]Department of Animal Science, Chungbuk National University, Cheongju, Korea
[2]Department of Biotechnology, Addis Ababa Science and Technology University, P.O. Box 16417, Addis Ababa, Ethiopia
[3]International Livestock Research Institute (ILRI), P.O. Box 5689, Addis Ababa, Ethiopia

Abstract

The objective of the study was to identify signatures of divergent selection associated with production and adaptive traits in Ethiopian and Hanwoo cattle by using a high-density and informative SNPs (80K) specifically developed from *Bos indicus* breeds. The most highly differentiated regions representing the top 1% windows were used to define genomic regions under divergent selection. Based on population genetic differentiation (F_{ST}) analysis, a total of 334 genes were identified in the comparison of Ethiopian cattle with Korean cattle (Hanwoo). The genes are associated with thermo-tolerance (*DNAJB5/Hsp40*), pigmentation (*ALX3, DCTN2, and MYO1A*), reproduction/fertility (*INHBC, UBE2D3, ID3, PAIP2, and PSPC1*), and body stature and production traits (*MBP2, HERC3, and GJB3 and POLR2A*) and carcass quality (*TFEC, MYOT, and PARPA*). Functional enrichment analysis further showed that the candidate genes were associated with pathways relevant for physiological adaptation, including vasopressin-regulated water reabsorption, Rap1 signaling, PIK3 signaling, and melanogenesis to extreme environments. By comparing cattle breeds with distinct evolutionary and breeding legacies, we spotted candidate genes under selection and pathways which may contribute to further understanding of the consequence of natural and/or artificial selection in molding the phenotypic diversity of modern cattle breeds.

Keywords : *Bos indicus*, Hanwoo, candidate genes, high-density SNPs, Indicus chip

Introduction

Bos taurus and *Bos indicus* cattle were domesticated independently in Near East and in Indian sub-continent from aurochs subspecies, respectively (Loftus et al., 1994). African cattle breeds were originated in Asia with a large introgression from wild African auroch (Decker et al., 2014). Since their introduction into the content, African cattle have been exposed to a range of new and changing environments and human selective breeding (Hanotte et al., 2010). Due to its geographical proximity to the Horn and East Coast, Ethiopia is served as a genetic corridor for cattle introduction to the continent and center of hybridization (Hanotte et al., 2010). Ethiopia hosts more than 24 diversified cattle populations or strains which are largely composed of indicine genetic background (Rege, 1999, Hanotte et al., 2002, Edea et al.,

---

***Corresponding author:** Kwan-Suk Kim.
Tel: +82-43-261-2547, Fax: +82-43-273-2240, E-mail: kwanskim@chungbuk.ac.kr
Received: 30 August, 2018, **Revised:** 21 September, 2018, **Accepted:** 21 September, 2018

2015b). These cattle populations show striking variation in terms of morphology, coat colors, and production traits, which may reflect adaptation of the sub-populations to the prevailing diverse local environmental conditions. Cattle populations such as Borana, Begait and Ogaden are adapted to low-altitude areas with high annual temperatures (12 to 37 °C (23 years of data), low rainfall varying from 594 to 747 mm/years (27 years data), whereas other cattle populations (Arsi, Guraghe, Arado, and Fogera) are mainly distributed mid to high-altitude areas characterized by high rainfall (721 to 1360 mm/year) and relatively low annual temperature (7 to 27°C). On the other hand, over the last few years, Hanwoo cattle have been selected for beef traits, including carcass weight, eye muscle area, backfat thickness, and marbling score (Lee et al., 2014). Specifically, a yearling weight was increased from 315.54 kg to 355.06 kg over the last 13 years (Park et al., 2013). Hence, selection for environmental adaptation and commercial traits may have differently shaped the genome of these cattle breeds.

The availability of genome high-density single nucleotide polymorphisms (SNPs) has facilitated the mapping of signatures selection associated with domestication and selection. Several investigations have been performed to map selection sweeps in cattle (Bahbahani et al., 2017, Bahbahani et al., 2015a, Chan et al., 2010, Makina et al., 2015a). Evidence of positive selection for ecological adaptation has also been investigated in human (Scheinfeldt et al., 2012), sheep and goats (Lv et al., 2014, Kim et al., 2015) and pig (Ai et al., 2013). With the exception of few emerging case studies, the evidence of selection for local adaptation is limited in African cattle population in general and in Ethiopian cattle in particular. Moreover, selection signatures mapping and diversity studies in African cattle or zebu have been mainly performed using Illumina Bovine SNP50K BeadChip (Bahbahani et al., 2015a, Makina et al., 2015b, Edea et al., 2014, Randhawa et al., 2016), which were derived from western commercial cattle breeds. As well demonstrated in our previous studies, taurine origin chips were less informative in African zebu cattle and led to bias estimation of populations parameters compared to the indicine derived SNPs (Edea et al., 2013, Edea et al., 2015a, Edea et al., 2015c). In this study, we used a high density and informative SNPs (80K) specifically developed from *Bos indicus* breeds to identify divergent selection between Ethiopian and Hanwoo cattle.

Materials and Methods

Cattle breeds, SNP genotyping and Quality Control

We sampled 8 Ethiopian cattle populations (n = 245), and taurine reference breed Hanwoo (n = 22). The Ethiopian cattle samples represented 4 traditional breed groups: sanga (Raya-Azebo), zenga (Fogera and Arado), zebu (Begait, Borana, Arsi, Guraghe, and Ogaden). Unelated animals were sampled from multiple herds and villages. Nasal samples were collected using Performagene LIVESTOCK's nasal swab DNA collection kit (DNA Genotek Inc., Kanata, ON, Canada). The Hanwoo (Korean cattle) samples were collected from commercial Hanwoo production farms.

All animals were genotyped using the 80K Indicine BeadChip (GeneSeek Genomic profiler; GeneSeek, Lincoln, NE, USA) derived mainly from *Bos indicus* breeds, which comprises 73,794 SNPs. Of 73,794

SNPs, we discarded 3,918 SNPs on the X chromosome, 74 on the Y–chromosome, 13 from mtDNA and 32 unmapped to any chromosome, leaving 69,758 autosomal SNPs mapped to the bovine genome. Autosomal markers were screened for the call rate <90% and minor allele frequency (MAF) <0.05. Additionally, in each population, individuals with a call rate < 90% were discarded. Finally, a total of 67,810 autosomal SNPs for 267 animals retained for the analysis. Quality control measures were performed using SNP and Variation Suite v8.5.0 (Golden Helix, Inc., Bozeman, MT, www.goldenhelix.com).

Detection of selection signals and functional analyses

The F_{ST} statistics for selection mapping has been widely applied in several studies, including in dog (Akey et al., 2010) and cattle (Ramey et al., 2013, Makina et al., 2015b, Bahbahani et al., 2015a). In order to search for genomic regions that have been under divergent selection in beef (Hanwoo) and Ethiopian cattle populations, genetic differentiation (F_{ST}) was calculated with unbiased estimator proposed by Weir & Cockerham (1984) using SNP and Variation Suite v8.5.0 (Golden Helix, Inc., Bozeman, MT, www.goldenhelix.com). To minimize the specious noise from single SNP based analyses, F_{ST} values were calculated with a sliding window of 10 SNPs as used in the previous study (Bahbahani et al., 2015b). As in (Porto-Neto et al., 2013), the most highly differentiated regions representing the top 1% windows of smoothed F_{ST} were treated as candidate selection regions. Genes within the specified selection regions were considered as candidate genes.

To annotate SNPs with respect to their functional classification of genes, we downloaded bovine gene annotation datasets (gene annotations and FASTA sequences) from the UCSC Genome Browser (http://genome.ucsc.edu/.). The SNPs were annotated using the ANNOVAR tool (Wang et al., 2010). Enriched pathways analyses were performed using the web-based DAVID Bioinformatics resources (v. 6.8, https://david.ncifcrf.gov/). Fisher's exact test (EASE score) less than 0.05 was used to examine the significant term as recommended by the software.

Results and Discussion

The average genomic F_{ST} values averaged in sliding windows of 10 SNPs (F_{ST}–10SNPW) was 0.20 between the Ethiopian cattle and Hanwoo. There are 334 genes within the top 1% windows (135 windows, Tables S1). Some of the regions on BTA7 (52.26–53.09 Mb), BTA12 (35.54–35.94 Mb), BTA13 (57.82–58.13 Mb), and BTA19 (27.32–27.81; 42.78–43.46 Mb) (Table S1) coincide with genomic regions under positive selection in East African shorthorn zebu cattle(Bahbahani et al., 2015a). Within these regions, three candidate genes (*EFHA1, ALOX12/ ALOX15,* and *SLC16A11*) concur with the present findings. *ALOX15* or *ALOX12* is near to QTL for scurs in cattle (Asai et al., 2004). Additionally, the candidate regions on BTA2 (64.62-64.93; 125.29-125.56 Mb), BTA7 (45.73-46.04; 50.62-50.98; 51.61-52.80 Mb), and BTA22 (36.62-37.03Mb) overlap with selection signals identified in West- African cattle breeds (Gautier et al., 2009).

Ethiopian cattle are evolved to adapt to a wide range of stresses (extreme temperature, UV, diseases prevalence, feed scarcity) and natural selection may have left genomic footprints in the underlying genes involved in local adaptation. Interestingly, we detected *DNAJB5* (*Hsp40*) gene on BTA8:59.58-59.99 which is known to be associated with thermo-tolerance (Table 1). Increased expression of *Hsp40* is observed in goat during hyperthermic condition (Archana et al., 2017). Further evidence suggests that *Hsp40* interact with *Hsp70* (Liberek & Georgopoulos, 1993, Schröder et al., 1993). Increased expression of the *Hsp40* genes was observed in *Drosophila melanogaster* subjected to heat-shock (Carmel et al., 2011). In addition to their well-known function of HSPs as molecular chaperones, recent evidence shows that the two heat shock proteins (*HSP70* and *HSP40*) also involved in antiviral immune responses (Dong et al., 2006). A QTL for body temperature has mapped on TA18 (Howard et al., 2014). The candidate gene *LOC10029917*1 overlapped with this region.

The adverse influence of heat stress on reproduction is less pronounced in *Bos indicus* than in *Bos taurus* (Paula-Lopes et al., 2013). These differences could be genetic and some of the top 1% windows harbor genes which are involved in embryonic development, or fertility, including *ID3, INHBC, UBE2D3, PSPC1, STAT5A, and PAIP2* (Table 1). INHBC is implied as the candidate gene for inhibin (IN) regulation, which is associated with testicular size and fertility in cattle (Fortes et al., 2013, Porto-Neto et al., 2014b). The gene *ID3* plays a vital role in the regulation of pre-implantation embryo development (Li et al., 2012a). Gene expression studies in high and low fertility heifers have revealed that *UBE2D3* is linked to fertility (Killeen et al., 2014). *PAIP2* was detected as under selection and associated with the reproductive traits in goats (Guan et al., 2016). *PSPC1* is abundantly expressed in the mouse testis and implicated in regulating nuclear events during spermatogenesis (Myojin et al., 2004). *STAT5A* contains QTL for early embryonic survival (Khatib et al., 2008), associated with fertilization rate (Khatib et al., 2009), and sire conception rate (Li et al., 2012b).

Ethiopian cattle populations are better survived and produce under high diseases and parasites loads. Four of the candidate genes (*AHCYL1, FAM13A, HERC3, PCID2, and CRYL1*) (Table 1) are related to the mastitis and somatic cell count in dairy breeds. In their study (Bonnefont *et al.*, 2011) demonstrated that

Table 1. Candidate genes identified in the comparison of Ethiopian cattle with Hanwoo

BTA	Position	Gene	Trait/Gene function
2	129.60-130.15	*ID3*	Pre-implantation embryo development (Li et al., 2012a).
3	33.45–33.68	*AHCYL1, ALX3*	Mastitis and pigmentation (Bonnefont et al., 2011)
5	56.23–56.34	*INHB, DCTN2*	Testicular size and fertility (Fortes et al., 2013, Porto-Neto et al., 2014b) and pigmentation (Gutiérrez-Gil et al., 2007).
5	56.70–56.79	*MYO1A*	Pigmentation (Gutiérrez-Gil et al., 2007)
6	37.44–37.70	*FAM13A, HERC3*	Somatic cell counts (Kowalewska-Luczak & Kulig, 2013); yearling weight and carcass quality traits (Porto-Neto et al., 2014b)
7	44.58–44.94	*THEG*	Spermatogenesis (Yanaka *et al*., 2000)
7	50.62-50.98	*MYOT*	Carcass quality(Adoligbe et al., 2016)
7	51.61–53.09	*UBE2D3, PAIP2, TFEC*	Fertility (Labrecque et al., 2013), carcass quality (Mokry et al., 2013)
8	59.58–59.99	*DNAJB5 (Hsp40)*	Thermo- tolerance, fertility (Carmel et al., 2011)
12	36.37–36.88	*PSPC1*	Male fertility/Spermatogenesis (Pan *et al*., 2005).
12	36.37-37.08	*PARPA*	role in regulating adipogenesis [32].
12	36.37-36.66	*GJA3*	Body size and development (Kim et al., 2016)
12	35.97–36.29	*CRYL1*	Somatic cell count (Bonnefont et al., 2011)
12	90.55–90.80	*PCID2*	Somatic cell count (Bonnefont et al., 2011)
13	49.23–49.58	*BMP2*	Body size and development (Kim et al., 2016)
19	27.32–28.04	*POLR2A*	Stature (Randhawa et al., 2015)

AHCYL1, PCID2, and *CRYL1* genes were differentially expressed between mastitis resistant and susceptible lines of dairy sheep. Similarly, variation within in the *FAM13A* gene was reported to be related to increased levels of somatic cell counts in Jersey cattle (Kowalewska-Luczak & Kulig, 2013).

Ethiopian cattle population show striking variation in terms of coat color, whereas Hanwoo cattle predominantly display brown coat color(Choi et al., 2012). Accordingly, we detected genes related to coat color phenotypes (*ALX3, DCTN2, and MYO1A* (Table 1)). It has been shown that *Alx3*-mediated repression of *Mitf* in rodents (Mallarino et al., 2016). *MITF* is a master regulator of melanocyte differentiation (Hou & Pavan, 2008) and known to influence white spotting patterns in cattle (Qanbari et al., 2014), swap buffalo (Yusnizar et al., 2015), horses (Hauswirth et al., 2012), and dogs (Rothschild et al., 2006). Additionally, the candidate region on BTA6 (37.44–37.70 Mb) overlaps with QTL for the degree of spotting in cattle (Reinsch et al., 1999). MYO1A and *DCTN2* are reported to have an influence on pigmentation in Charolais × Holstein population (Gutiérrez-Gil et al., 2007). The regions on BTA5 (56.59-56.70 Mb) and BTA6 (29.72–30.03 Mb) contain QTLs for coat color and coat texture (Liu et al., 2009, Mészáros et al., 2015, Huson et al., 2014). Given the importance of coat color and texture in thermoregulation (Gebremedhin & Wu, 2001); these genes are potential candidates for zebu adaptation to hot tropical areas.

Our gene functional enrichment analysis revealed important pathways that may be involve in African cattle adaptation under tropical hot environments, including “vasopressin-regulated water reabsorption” (*P = 0.001*), “Rap1 signaling” (*P = 0.011*), “PI3K-Akt signaling” (*P = 0.035*), and “melanogenesis” (*P = 0.007*, Table 2). Water reabsorption is one of the physiological mechanisms for animal adaptation under dry habitats (CAIN III *et al.*, 2006). A recent study involving Chinese sheep breeds evolved under arid environments detected highly enriched biological pathways for water reabsorption (Yang *et al.*, 2016). In cattle, heat stress increased reactive oxygen species (ROS) formation at 40 °C (Singh *et al.*, 2014). Generation of ROS is a response to stress conditions (Pastori & Foyer, 2002). The Rap1 signal was involved in the suppression of Ras-generated reactive oxygen species and protection against oxidative stress (Remans et al., 2004). The PI3K signaling pathway plays an important role in *Hsp90* chaperone function

Table 2. Results of enriched functional pathyas of the candidate genes

Term	Count	Fisher Exact
Pathways in cancer	17	0.00045
Ubiquitin mediated proteolysis	8	0.0023
Hepatitis B	8	0.0038
Vasopressin-regulated water reabsorption	5	0.0011
Rap1 signaling pathway	9	0.011
Melanogenesis	6	0.0069
Chagas disease (American trypanosomiasis)	6	0.013
Amoebiasis	6	0.012
Endocytosis	9	0.034
Signaling pathways regulating pluripotency of stem cells	6	0.032
PI3K-Akt signaling pathway	11	0.035
Estrogen signaling pathway	5	0.026
Hedgehog signaling pathway	3	0.0086
Adrenergic signaling in cardiomyocytes	6	0.037
Platelet activation	6	0.022

through regulating the expression of heat shock protein (*Hsp70*) (Chatterjee *et al.*, 2013, Tu et al., 2000). Thus, these pathways are likely relevant for Ethiopian cattle adaptation under stressful environments.

Compared with Ethiopian cattle populations which are characterized by a short stature, and low productivity, Hanwoo cattle have undergone selection for yearling weight and beef quality traits, including carcass weight, eye muscle area, and backfat thickness (Lee et al., 2012, Flori et al., 2009). Intriguingly, we detected some candidate genes (*TFEC, HERC3, POLR2A, BMP2, GJA3, PARP4,* and *MYOT*) (Table 1) within the top 1% windows related to stature, body size, and beef quality traits. *TFEC and HERC3* are associated with a backfat thickness and yearling weight in beef cattle, respectively (Mokry et al., 2013, Porto-Neto et al., 2014a). Polymerase (RNA) II (DNA directed) polypeptide A (*POLR2A*) contains functional variants contributing to the genetic control of bovine stature (Randhawa et al., 2015). *BMP2* and *GJA3* are well-known genes for body size and development (Fan et al., 2011) and undergone selection in sheep and goat breeds adapted to hot arid environments (Kim et al., 2016). More importantly, the *GJA3* gene is identified as under recent selection in brown Hanwoo cattle (Lim et al., 2016). Genetic variation within the *PARP4* has found to be associated with carcass weight in commercial Hanwoo cattle (Edea et al., 2018) and regulates adipogenesis. *MYOT* is involved in myofibril assembly and actin binding in the muscle tissue (Schessl et al., 2014). Recent functional analysis revealed the association of mutations within *MYOT* with loin muscle area, backfat thickness and intramuscular fat in cattle (Adoligbe et al., 2016).

In conclusion, by comparing cattle breeds with distinct evolutionary and breeding legacies, we

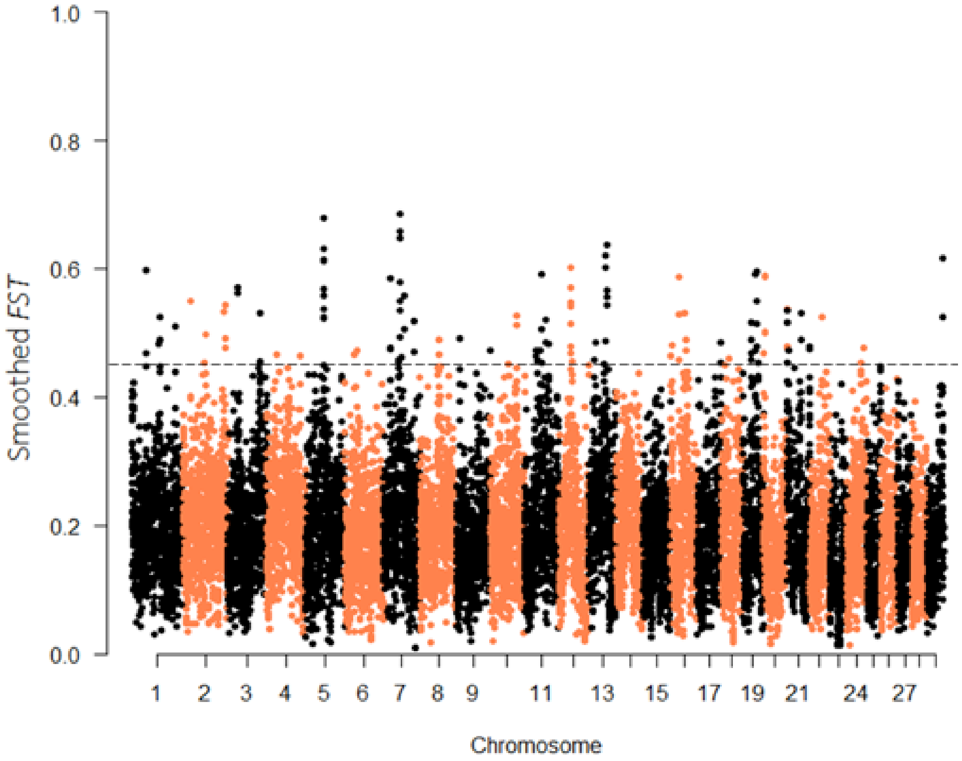

Fig. 1. Manhattan plots of genome-wide smoothed F_{ST} values. The dotted gray line indicates the top 1% F_{ST} values of the genome-wide empirical distribution.

identified candidate genes under directional selection and pathways which may contribute to further understanding of the consequence of natural and/or artificial selection in shaping the diversity of modern cattle breeds.

Conflict of Interest

The authors declare that there is no conflict of interest with any financial organization concerning the material discussed in the manuscript.

Acknowledgements

This study was supported by the grant from Korea Institute of Planning and Evaluation for Technology in Food, Agriculture, Forestry and Fisheries (No. 318015031SB010) in Korea.

References

Adoligbe, C., L. Zan and S. Farougou. 2016. P3017 Functional analysis and association studies of bovine *MYOT* gene with meat quality. J *Anim Sci*, 94: 59-60.

Ai, H., L. Huang and J. Ren, 2013: Genetic Diversity, Linkage Disequilibrium and Selection Signatures in Chinese and Western Pigs Revealed by Genome-Wide SNP Markers. *PLoS ONE*, 8, e56001.

Akey, J. M., A. L. Ruhe, D. T. Akey, A. K. Wong, C. F. Connelly, J. Madeoy, T. J. Nicholas and M. W. Neff. 2010. Tracking footprints of artificial selection in the dog genome. *Proc Natl Acad Sci U.S.A.*107: 1160-1165.

Archana, P., J. Aleena, P. Pragna, M. Vidya, A. Niyas, M. Bagath, G. Krishnan, A. Manimaran, V. Beena and E. Kurien., 2017. Role of heat shock proteins in livestock adaptation to heat stress. *J Dairy Vety Anim Res*. 5: 00127.

Asai, M., T. G. Berryere and S. M. Schmutz. 2004. The scurs locus in cattle maps to bovine chromosome 19. *Animl Genet.* 35: 34-39.

Bahbahani, H., H. Clifford, D. Wragg, M. N. Mbole-Kariuki, C. Van Tassell, T. Sonstegard, M. Woolhouse and O. Hanotte. 2015a. Signatures of positive selection in East African Shorthorn Zebu: A genome-wide single nucleotide polymorphism analysis. *Scientific Reports,* 5, 11729.

Bahbahani, H., H. Clifford, D. Wragg, M. N. Mbole-Kariuki, C. Van Tassell, T. Sonstegard, M. Woolhouse and O. Hanotte. 2015b. Signatures of positive selection in East African Shorthorn Zebu: A genome-wide single nucleotide polymorphism analysis. Sci Rep.5: 11729.

Bahbahani, H., A. Tijjani, C. Mukasa, D. Wragg, F. Almathen, O. Nash, G. N. Akpa, M. Mbole-Kariuki, S. Malla and M. Woolhouse. 2017. Signatures of Selection for Environmental Adaptation and Zebu× Taurine Hybrid Fitness in East African Shorthorn *Zebu. Front Genet.* 8: 68.

Bonnefont, C. M., M. Toufeer, C. Caubet, E. Foulon, C. Tasca, M.-R. Aurel, D. Bergonier, S. Boullier, C. Robert-Granié, G. Foucras and R. Rupp. 2011. Transcriptomic analysis of milk somatic cells in mastitis resistant and susceptible sheep upon challenge with Staphylococcus epidermidis and Staphylococcus aureus. *BMC Genomics*. 12: 1-16.

CAIN III, J. W., P. R. Krausman, S. S. Rosenstock and J. C. Turner. 2006. Mechanisms of thermoregulation and water balance in desert ungulates. *Wildl Soc Bull*. 34: 570-581.

Carmel, J., E. Rashkovetsky, E. Nevo and A. Korol. 2011. Differential expression of small heat shock protein genes Hsp23 and *Hsp40*, and heat shock gene Hsr-omega in fruit flies (Drosophila melanogaster) along a microclimatic gradient. *J Hered*. 102: 593-603.

Chan, E. K., S. H. Nagaraj and A. Reverter. 2010. The evolution of tropical adaptation: comparing taurine and zebu cattle. *Anim Genet*. 41: 467-477.

Chatterjee, M., M. Andrulis, T. Stühmer, E. Müller, C. Hofmann, T. Steinbrunn, T. Heimberger, H. Schraud, S. Kressmann, H. Einsele and R. C. Bargou. 2013. The PI3K/Akt signaling pathway regulates the expression of *Hsp70*, which critically contributes to *Hsp90*-chaperone function and tumor cell survival in multiple myeloma. *Haematologica* 98: 1132-1141.

Choi, T. J., S. S. Lee, D. H. Yoon, H. S. Kang, C. D. Kim, I. H. Hwang, C. Y. Kim, X. Jin, C. G. Yang and K. S. Seo. 2012. Determination of Genetic Diversity among Korean Hanwoo Cattle Based on Physical Characteristics. *Asian-Austral J Anim Sci*. 25: 1205-1215.

Decker, J. E., S. D. McKay, M. M. Rolf, J. Kim, A. Molina Alcalá, T. S. Sonstegard, O. Hanotte, A. Götherström, C. M. Seabury, L. Praharani, M. E. Babar, L. Correia de Almeida Regitano, M. A. Yildiz, M. P. Heaton, W.-S. Liu, C.-Z. Lei, J. M. Reecy, M. Saif-Ur-Rehman, R. D. Schnabel and J. F. Taylor. 2014. Worldwide Patterns of Ancestry, Divergence, and Admixture in Domesticated Cattle. *PLoS Genet.* 10: e1004254.

Dong, C.-W., Y.-B. Zhang, Q.-Y. Zhang and J.-F. Gui. 2006. Differential expression of three Paralichthys olivaceus *Hsp40* genes in responses to virus infection and heat shock. *Fish & Shellfish Immunol.* 21: 146-158.

Edea, Z., M. Bhuiyan, T. Dessie, M. Rothschild, H. Dadi and K. Kim. 2015a. Genome-wide genetic diversity, population structure and admixture analysis in African and Asian cattle breeds. *Animal* 9: 218-226.

Edea, Z., M. S. A. Bhuiyan, T. Dessie, M. F. Rothschild, H. Dadi and K. S. Kim. 2015b. Genome-wide genetic diversity, population structure and admixture analysis in African and Asian cattle breeds. *Animal,* 9, 218-226.

Edea, Z., H. Dadi, T. Dessie, S.-H. Lee and K.-S. Kim. 2015c. Genome-wide linkage disequilibrium analysis of indigenous cattle breeds of Ethiopia and Korea using different SNP genotyping BeadChips. *Genes Genom,* 37, 759-765.

Edea, Z., H. Dadi, S.-W. Kim, T. Dessie, T. Lee, H. Kim, J.-J. Kim and K.-S. Kim. 2013. Genetic diversity, population structure and relationships in indigenous cattle populations of Ethiopia and Korean Hanwoo breeds using SNP markers. *Front Genet*. 4.

Edea, Z., H. Dadi, S. W. Kim, J. H. Park, G. H. Shin, T. Dessie and K. S. Kim. 2014. Linkage disequilibrium and genomic scan to detect selective loci in cattle populations adapted to different ecological conditions in Ethiopia. *J Anim Breed Genet*. 131, 358-366.

Edea, Z., Y. H. Jeoung, S. S. Shin, J. Ku, S. Seo, I. H. Kim, S. W. Kim and K. S. Kim. 2018. Genome-wide association study of carcass weight in commercial Hanwoo cattle. *Asian-Austral J Anim Sci*. 31: 327-334.

Fan, B., S. K. Onteru, Z. Q. Du, D. J. Garrick, K. J. Stalder and M. F. Rothschild. 2011. Genome-wide association study identifies Loci for body composition and structural soundness traits in pigs. *PLoS One* 6: e14726.

Flori, L., S. Fritz, F. Jaffrezic, M. Boussaha, I. Gut, S. Heath, J. L. Foulley and M. Gautier. 2009. The genome response to artificial selection: a case study in dairy cattle. *PLoS One*, 4, e6595.

Fortes, M. R. S., A. Reverter, M. Kelly, R. McCulloch and S. A. Lehnert. 2013. Genome-wide association study for inhibin, luteinizing hormone, insulin-like growth factor 1, testicular size and semen traits in bovine species. *Andrology* 1, 644-650.

Gautier, M., L. Flori, A. Riebler, F. Jaffrezic, D. Laloe, I. Gut, K. Moazami-Goudarzi and J. L. Foulley. 2009. A whole genome Bayesian scan for adaptive genetic divergence in West African cattle. *BMC Genomics* 10: 550.

Gebremedhin, K. G. and B. Wu, Sensible and latent heat losses from wet-skin surface and fur layer. in Proceedings of the ASAE Annual International Meeting, Sacramento, CA. ASAE Paper, 2001.

Guan, D., N. Luo, X. Tan, Z. Zhao, Y. Huang, R. Na, J. Zhang and Y. Zhao. 2016. Scanning of selection signature provides a glimpse into important economic traits in goats (Capra hircus). *Sci Rep*. 6: 36372.

Gutiérrez-Gil, B., P. Wiener and J. L. Williams. 2007. Genetic effects on coat colour in cattle: dilution of eumelanin and phaeomelanin pigments in an F2-Backcross Charolais × Holstein population. *BMC Genet*., 8: 56-56.

Hanotte, O., D. G. Bradley, J. W. Ochieng, Y. Verjee, E. W. Hill and J. E. Rege. 2002. African pastoralism: genetic imprints of origins and migrations. *Science* 296.

Hanotte, O., T. Dessie and S. Kemp. 2010. Time to tap Africa's livestock genomes. *Science*(*Washington*), 328, 1640-1641.

Hauswirth, R., B. Haase, M. Blatter, S. A. Brooks, D. Burger, C. Drögemüller, V. Gerber, D. Henke, J. Janda and R. Jude, 2012: Mutations in *MITF* and PAX3 cause “splashed white” and other white spotting phenotypes in horses. *PLoS Genet.* 8: e1002653.

Hou, L. and W. J. Pavan. 2008. Transcriptional and signaling regulation in neural crest stem cell-derived melanocyte development: do all roads lead to Mitf? *Cell Res*. 18: 1163.

Howard, J. T., S. D. Kachman, W. M. Snelling, E. J. Pollak, D. C. Ciobanu, L. A. Kuehn and M. L. Spangler. 2014. Beef cattle body temperature during climatic stress: a genome-wide association study. *Int J Biometeorol*. 58: 1665-1672.

Huson, H. J., E.-S. Kim, R. W. Godfrey, T. A. Olson, M. C. McClure, C. C. Chase, R. Rizzi, A. M. O'Brien, C. P. Van Tassell and J. F. Garcia. 2014. Genome-wide association study and ancestral origins of the slick-hair coat in tropically adapted cattle. *Front Genet*. 5.

Khatib, H., W. Huang, X. Wang, A. H. Tran, A. B. Bindrim, V. Schutzkus, R. L. Monson and B. S. Yandell. 2009. Single gene and gene interaction effects on fertilization and embryonic survival rates in cattle. *J Dairy Sci*. 92, 2238-2247.

Khatib, H., R. L. Monson, V. Schutzkus, D. M. Kohl, G. J. Rosa and J. J. Rutledge. 2008. Mutations in the *STAT5A* gene are associated with embryonic survival and milk composition in cattle. *J Dairy Sci*. 91, 784-793.

Killeen, A. P., D. G. Morris, D. A. Kenny, M. P. Mullen, M. G. Diskin and S. M. Waters. 2014. Global gene expression in endometrium of high and low fertility heifers during the mid-luteal phase of the estrous cycle. *BMC Genomics* 15, 1.

Kim, E. S., A. R. Elbeltagy, A. M. Aboul-Naga, B. Rischkowsky, B. Sayre, J. M. Mwacharo and M. F. Rothschild. 2016. Multiple genomic signatures of selection in goats and sheep indigenous to a hot arid environment. *Heredity* 116: 255-264.

Kowalewska-Luczak, I. and H. Kulig. 2013. Polymorphism of the *FAM13A*, ABCG2, OPN, LAP3, HCAP-G, PPARGC1A genes and somatic cell count of Jersey cows--preliminary study. Res Vet Sci.94: 252-255.

Labrecque, R., C. Vigneault, P. Blondin and M. A. Sirard. 2013. Gene Expression Analysis of Bovine Oocytes With High Developmental Competence Obtained From FSH - Stimulated Animals. *Mol R ep Dev*. 80: 428-440.

Lee, J. H., Y. Li and J. J. Kim. 2012. Detection of QTL for Carcass Quality on Chromosome 6 by Exploiting Linkage and Linkage Disequilibrium in Hanwoo. *Asian Australas J Anim Sci*. 25: 17-21.

Li, G., K. Khateeb, E. Schaeffer, B. Zhang and H. Khatib. 2012a. Genes of the transforming growth factor-beta signalling pathway are associated with pre-implantation embryonic development in cattle. *J Dairy Res*. 79: 310-317.

Li, G., F. Penagaricano, K. A. Weigel, Y. Zhang, G. Rosa and H. Khatib. 2012b. Comparative genomics between fly, mouse, and cattle identifies genes associated with sire conception rate. *J Dairy Sci*. 95: 6122-6129.

Liberek, K. and C. Georgopoulos. 1993. Autoregulation of the Escherichia coli heat shock response by the DnaK and DnaJ heat shock proteins. *Proc Natl Acad Sci U.S.A.* 90: 11019-11023.

Lim, D., B. H. Choi, Y. M. Cho, H. H. Chai, G. W. Jang, C. Gondro, Y. H. Jeoung and S. H. Lee. 2016. Analysis of extended haplotype in Korean cattle (Hanwoo) population. *BMB reports*, 49, 514.

Liu, L., B. Harris, M. Keehan and Y. Zhang. 2009. Genome scan of pigmentation traits in Friesian-Jersey crossbred cattle. *J Genet Genomics*, 36, 661-666.

Loftus, R. T., D. E. MacHugh, D. G. Bradley, P. M. Sharp and P. Cunningham. 1994. Evidence for two independent domestications of cattle. *Proc Natl Acad Sci U.S.A.* 91: 2757-2761.

Lv, F. H., S. Agha, J. Kantanen, L. Colli, S. Stucki, J. W. Kijas, S. Joost, M. H. Li and P. Ajmone Marsan.2014. Adaptations to climate-mediated selective pressures in sheep. *Mol Biol Evol*. 31: 3324-3343.

Makina, S. O., F. C. Muchadeyi, E. Marle-Köster, J. F. Taylor, M. L. Makgahlela and A. Maiwashe. 2015a. Genome-wide scan for selection signatures in six cattle breeds in South Africa. *Genet Sel Evo*l. 47: 92.

Makina, S. O., F. C. Muchadeyi, E. van Marle-Koster, J. F. Taylor, M. L. Makgahlela and A. Maiwashe.2015b. Genome-wide scan for selection signatures in six cattle breeds in South Africa. *Genet Sel Evo*l. 47: 92.

Mallarino, R., C. Henegar, M. Mirasierra, M. Manceau, C. Schradin, M. Vallejo, S. Beronja, G. S. Barsh and H. E. Hoekstra. 2016. Developmental mechanisms of stripe patterns in rodents. *Nature*, 539, 518-523.

Mészáros, G., E. Petautschnig, H. Schwarzenbacher and J. Sölkner. 2015. Genomic regions influencing coat color saturation and facial markings in Fleckvieh cattle. *Anim Genet*. 46: 65-68.

Mokry, F. B., R. H. Higa, M. de Alvarenga Mudadu, A. O. de Lima, S. L. C. Meirelles, M. V. G. B. da Silva, F. F. Cardoso, M. M. de Oliveira, I. Urbinati and S. C. M. Niciura. 2013. Genome-wide association study for backfat thickness in Canchim beef cattle using Random Forest approach. *BMC Genet*. 14: 47.

Myojin, R., S. Kuwahara, T. Yasaki, T. Matsunaga, T. Sakurai, M. Kimura, S. Uesugi and Y. Kurihara.2004. Expression and functional significance of mouse paraspeckle protein 1 on spermatogenesis. *Biol Reprod*. 71: 926-932.

Pan, J., M. Goodheart, S. Chuma, N. Nakatsuji, D. C. Page and P. J. Wang. 2005. RNF17, a component of the mammalian germ cell nuage, is essential for spermiogenesis. *Development (Cambridge, England),* 132: 4029-4039.

Pastori, G. M. and C. H. Foyer. 2002. Common Components, Networks, and Pathways of Cross-Tolerance to Stress. The Central Role of "Redox" and Abscisic Acid-Mediated Controls. *Plant Physiol*. 129: 460-468.

Paula-Lopes, F. F., R. S. Lima, R. A. Satrapa and C. M. Barros. 2013. Physiology and Endocrinology Symposium: influence of cattle genotype (*Bos indicus* vs. *Bos taurus*) on oocyte and preimplantation embryo resistance to increased temperature. *JAnim Sci*., 91: 1143-1153.

Porto-Neto, L. R., A. Reverter, K. C. Prayaga, E. K. Chan, D. J. Johnston, R. J. Hawken, G. Fordyce, J. F. Garcia, T. S. Sonstegard, S. Bolormaa, M. E. Goddard, H. M. Burrow, J. M. Henshall, S. A. Lehnert and W. Barendse. 2014a. The genetic architecture of climatic adaptation of tropical cattle. *PLoS One* 9: e113284.

Porto-Neto, L. R., A. Reverter, K. C. Prayaga, E. K. F. Chan, D. J. Johnston, R. J. Hawken, G. Fordyce, J. F. Garcia, T. S. Sonstegard, S. Bolormaa, M. E. Goddard, H. M. Burrow, J. M. Henshall, S. A. Lehnert and W. Barendse. 2014b. The Genetic Architecture of Climatic Adaptation of Tropical Cattle. *PLOS ONE* 9: e113284.

Porto-Neto, L. R., T. S. Sonstegard, G. E. Liu, D. M. Bickhart, M. V. Da Silva, M. A. Machado, Y. T. Utsunomiya, J. F. Garcia, C. Gondro and C. P. Van Tassell., 2013. Genomic divergence of zebu and taurine cattle identified through high-density SNP genotyping. *BMC Genomics* 14: 876.

Qanbari, S., H. Pausch, S. Jansen, M. Somel, T. M. Strom, R. Fries, R. Nielsen and H. Simianer. 2014. Classic selective sweeps revealed by massive sequencing in cattle. *PLoS genetics*, 10, e1004148.

Ramey, H. R., J. E. Decker, S. D. McKay, M. M. Rolf, R. D. Schnabel and J. F. Taylor. 2013. Detection of selective sweeps in cattle using genome-wide SNP data. *BMC Genomics* 14: 1.

Randhawa, I. A. S., M. S. Khatkar, P. C. Thomson and H. W. Raadsma. 2015. Composite Selection Signals for Complex Traits Exemplified Through Bovine Stature Using Multibreed Cohorts of European and African *Bos taurus*. *G3 (Bethesda)* 5: 1391-1401.

Randhawa, I. A. S., M. S. Khatkar, P. C. Thomson and H. W. Raadsma. 2016. A Meta-Assembly of Selection Signatures in Cattle. *PLOS ONE* 11: e0153013.

Rege, J. 1999. The state of African cattle genetic resources I. Classification framework and identification of threatened and extinct breeds. *Anim Genet Res Inform*, 25, 1-25.

Reinsch, N., H. Thomsen, N. Xu, M. Brink, C. Looft, E. Kalm, G. A. Brockmann, S. Grupe, C. Kuhn, M. Schwerin, B. Leyhe, S. Hiendleder, G. Erhardt, I. Medjugorac, I. Russ, M. Forster, R. Reents and G. Averdunk. 1999. A QTL for the degree of spotting in cattle shows synteny with the KIT locus on chromosome 6. *J.Hered*. 90: 629-634.

Remans, P. H., S. I. Gringhuis, J. M. van Laar, M. E. Sanders, E. A. Papendrecht-van der Voort, F. J. Zwartkruis, E. W. Levarht, M. Rosas, P. J. Coffer, F. C. Breedveld, J. L. Bos, P. P. Tak, C. L. Verweij and K. A. Reedquist. 2004. Rap1 signaling is required for suppression of Ras-generated reactive oxygen species and protection against oxidative stress in T lymphocytes. *J Immunol*. 173, 920-931.

Rothschild, M., P. Van Cleave, K. Glenn, L. Carlstrom and N. Ellinwood. 2006. Association of *MITF* with white spotting in Beagle crosses and Newfoundland dogs. *Anim Genet*. 37: 606-607.

Scheinfeldt, L. B., S. Soi, S. Thompson, A. Ranciaro, D. Woldemeskel, W. Beggs, C. Lambert, J. P. Jarvis, D. Abate, G. Belay and S. A. Tishkoff. 2012. Genetic adaptation to high altitude in the Ethiopian highlands. *Genome Biol*.13: 1-9.

Schessl, J., E. Bach, S. Rost, S. Feldkirchner, C. Kubny, S. Müller, F.-G. Hanisch, W. Kress and B. Schoser. 2014. Novel recessive myotilin mutation causes severe myofibrillar myopathy. *Neurogenetics* 15, 151-156.

Schröder, H., T. Langer, F. Hartl and B. Bukau. 1993.DnaK, DnaJ and GrpE form a cellular chaperone machinery capable of repairing heat-induced protein damage. *The EMBO J*. 12: 4137.

Singh, A. K., R. C. Upadhyay, D. Malakar, S. Kumar and S. V. Singh. 2014. Effect of thermal stress on *HSP70* expression in dermal fibroblast of zebu (Tharparkar) and crossbred (Karan-Fries) cattle. *J Therm. Biol*. 43: 46-53.

Tu, Y., A. Gardner and A. Lichtenstein. 2000. The phosphatidylinositol 3-kinase/AKT kinase pathway in multiple myeloma plasma cells: roles in cytokine-dependent survival and proliferative responses. *Cancer Res*. 60: 6763-6770.

Wang, K., M. Li and H. Hakonarson. 2010. ANNOVAR: functional annotation of genetic variants from high-throughput sequencing data. Nucleic Acids Res. 38: e164-e164.

Yanaka, N., K. Kobayashi, K. Wakimoto, E. Yamada, H. Imahie, Y. Imai and C. Mori. 2000. Insertional mutation of the murine kisimo locus caused a defect in spermatogenesis. *J Biol Chem*. 275: 14791-14794.

Yang, J., W.-R. Li, F.-H. Lv, S.-G. He, S.-L. Tian, W.-F. Peng, Y.-W. Sun, Y.-X. Zhao, X.-L. Tu, M. Zhang, X.-L. Xie, Y.-T. Wang, J.-Q. Li, Y.-G. Liu, Z.-Q. Shen, F. Wang, G.-J. Liu, H.-F. Lu, J. Kantanen, J.-L. Han, M.-H. Li and M.-J. Liu. 2016. Whole-Genome Sequencing of Native Sheep Provides Insights into Rapid Adaptations to Extreme Environments. *Mol Biol Evol*. 33: 2576-2592.

Yusnizar, Y., M. Wilbe, A. O. Herlino, C. Sumantri, R. R. Noor, A. Boediono, L. Andersson and G. Andersson. 2015. Microphthalmia-associated transcription factor mutations are associated with white-spotted coat color in swamp buffalo. *Anim Genet*. 46: 676-682.