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RESEARCH ARTICLE

Genome-Wide Survey of Selection Signatures in Pakistani Cattle Breeds

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ABSTRACT

Selection signatures define a specific genome region, which is considered specific and important functional trait under natural or artificial selection. In this study, we used two different approaches to identify the selection signatures between and within ten different cattle breeds in Pakistan. The first method was used to detect haplotypes fixation on genomic regions within breeds. The second method, population differentiation index (Fst), was used to identify genomic regions having different allele frequencies between these cattle breeds. All selected breeds include Achi (18), Bhagnari (14), Cholistani (13), Dajal (10), Dhanni (10), Kankraj (12), Lohani (19), Red Sindhi (13), Sahiwal (14) and Tharparkar (13), were divided into three populations (A, B & C) based on nucleotide structural analysis. In this study, we identified fifty-three candidate genomic regions using both approaches. Seventeen genomic regions were common among three populations and forty-nine were successfully annotated with identification of some candidate genes. MCIR gene is found on BTA-18 between 14, 757, 332-14, 759, 082 bp. However, a number of putative genes linked with production traits (LAP3, CAPN3, CYP19, SAR1B and RPS6KA2), reproductive traits (PIK3CA, SPERT and IGF1R), nervous system (KIT, FGF5, ASIP and HSPB9) and immune response (IL2, IL4, SERPINA3-8 and BOLA3) are identified as being under selection. The finding of this preliminary selection signatures study in Pakistani cattle breeds provides a new insight for genomic diversity during domestication events and breed development. These results could be used to expedite the genomic assisted breeding selection in these breeds for the improvement of important economic related traits.

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INTRODUCTION

Humans domesticated cattle genetic resources nearly 8,000 to 10,000 years ago (Anderson and Georges, 2004). Approximately, 1,109 cattle breeds exist around the world (Porto-Neto *et al.*, 2014). Therefore, cattle diversity attracts significant opportunities to identify the variants, at phenotypes as well as at the genomic level, among the cattle breeds (Qanbari *et al.*, 2011). Currently, with the accessibility to high throughput SNPs technology along with powerful statistical tools make it possible to detect the genome wide selection signatures in livestock species (Simianer and Qanbari, 2014). A selection signature is considered as an important genetic based approach in farm animals, especially in cattle (Tang *et al*., 2007). It provides a wide picture of evolutionary processes as well as complex functional information in the genome (Kasarda *et al.*, 2015). This information helps in identification of effective loci for breeding programs and also for functional genomics annotation (Ismael *et al.*, 2016). These methods are based on allele frequencies spectrum or haplotypes segregations in a population (Vitti *et al*., 2013; Yi and Kim, 2015). These methods were used to identify those regions, which were affected during the

complex domestication process, breed development and specific trait selection (Ramey *et al.*, 2013). Some selective sweeps were identified in African zebu cattle on different chromosomes (Malkina *et al*., 2015). The Bovine Hap Map Consortium (2009) estimated the divergence of behavior, feed efficiency and immunology related candidate genes using Integrated Haplotype Score and population differentiation (Fst) method. Fst methods were used in Holstein cattle to detect 236 candidate genomic regions under positive selection (Qanbari *et al*., 2011). There is limited information about the genomic variation that triggers important economic and adaptive traits in Pakistani indigenous cattle breeds (Mustafa *et al*., 2017). Therefore, we conducted a whole genome selection signatures survey in ten cattle breeds in Pakistan to investigate the candidate genomic regions under selection during the complex evolutionary process and breed development.

MATERIALS AND METHODS

Genomic DNA and grouping of breeds: In this study, we used 136 samples from ten different cattle breeds (detail description of sampling is available in a previous study of Mustafa *et al*., 2017). All breeds were divided into three main populations based on structural analysis. Only autosomal SNPs were included for further analysis.

Identification of selection signatures: We used two different approaches to identify selection signatures. Firstly, we used selective sweep using minor allele frequencies (MAF) through a local reduction in genetic variation within each selected breed. The analyzed loci in each breed were 431,897 (Achi), 508,995 (Bhagnari), 510,898 (Cholistani), 533,996 (Dhanni), 498,898 (Dajal), 499,399 (Kankraj), 521,999 (Lohani), 499,798 (Red Sindhi), 500,968 (Sahiwal) and 502, 538 (Tharparkar) SNPs, respectively. Secondly, we used population differentiation (Fst) approach to identify the selection signatures in different breeds. Moreover, samples were also pruned for high LD SNPs using PLINK software version 1.9 (Purcell *et al.*, 2007) and remaining 250,469 SNPs were used for selection signatures identification using population differentiation (Fst) method (Akey *et al.*, 2002; Kasarda *et al.*, 2015). To reduce the heterozygosity level in the data set of all the breeds, we used LD pruning as reported in some European and African zebu cattle breeds (Malkina *et al*., 2015).

The combinations of the two methods (selective sweep and Fst) in fact increased the reliability of selection signatures studies (Ismael *et al.*, 2016). Therefore, we used two methods to identify a putative selection signature. First, we explored the complete fixation of haplotypes within each breed for strong recent signatures of selection (Malkina *et al*., 2015). The theory behind this approach is based upon the observation of intensive variant selection and eventually a comprehensive variation loss within the chromosomal regions (surrounds selected variants) which ultimately fixed haplotypes (Vitti *et al.*, 2013). Secondly, we searched SNPs with high Fst owing to distinctive selection history for different groups of animals, which cause distortions in the selected variable at allele frequency level in different breeds (Qanbari *et al*., 2011). Unbiased Fst were estimated using SVS (SNPs Variation Suite) version 8.0, among all three combinations for each SNP and sliding widows of four SNPs were used to calculate the average Fst. The smoothed Fst value of each compared population was plotted against chromosomal coordinates based on UMD 3.1 database.

Identification of candidate genome regions: Genome coordinates were detected in selected genomic regions using UCSC genome browser (Kent *et al.*, 2002; Lingyang *et al.*, 2015). PANTHER database was used to assess biological process and metabolic pathways in which detected genes are involved. Furthermore, the cattle quantitative trait loci (QTL) database was searched to find out any overlap with the previously reported cattle QTLs, within the candidate genome regions (Mi *et al*., 2013).

RESULTS

Descriptive statistics: Minor allele frequencies, polymorphic SNPs, and Hardy-Weinberg for all selected breeds are described in details in a previous study (Mustafa *et al*., 2017) and based on structural analysis all individuals were divided into three populations. Putative selective sweeps of each selected population were detected using the haplotypes fixation test and fourteen candidate genomic regions were detected on thirteen chromosomes (Table 1). Ten putative selection signatures were detected as population specific and four were common among populations. One candidate selection signature was common between populations A and C on BTA-05 and three were detected between populations B and C on BTA-14, -16 and -20 (Fig. 1). The average population specific selective sweeps size was 164.34 that ranged from 16.9 kb to 448.87 kb.

Segregated candidate genome regions: Genome wide distribution of Fst value across all autosomal SNPs were assembled to calculate the allele frequency between loci and observed skewed towards small Fst value. Approximately 35% SNPs had Fst value 0.05 and only 2% SNPs had Fst value 0.25. Thirty-nine candidate genomic regions were identified and were found disseminated across 19 chromosomes using population differentiation (Fst) method. These regions suggest that approximately 9.7 Mb of bovine sequences are under strong selection in these three cattle populations. The candidate genome region was spanning about 123.52 kb averaged size. However, the major genomic portion was observed between group C vs. others on chromosome 09 (613.31 kb) between 46, 632, 366–47, 246, 008, while the smallest genomic region was also observed between the group C vs. others on chromosome 08 (10.21kb) between 60, 368, 097-60, 379, 016 bp. The Fst peak number per chromosomes varied from 0-2 across all these comparison. Thirteen differentiated regions (BTA 6, 9, 10, 12, 13, 16, 18, 21 and 23) were common among these combinations, with the B vs. others; C vs. others combinations shared most differentiated genomic portions (07), while A vs. B & C, C vs. others had the lowest number (03).

Table 1: Candidate genes within detected selective sweeps regions within breeds

Group*	Chr.	Position	SNPs No.	Size (kb)	Candidate genes	Traits
C	1	76685699-76721920	7	36.22	OSTN	An inhibitor of osteoblast
A	2	127125973-127172772	5	46.89	FABP3	Milk fat synthesis in mammary gland
B	4	93249874-93266724	6	16.90	LEP	Growth and fat deposition
A & C	5	28859701-29043611	8	183.91	HOXC13	Udder height, intramuscular fat
C	6	102546791-102779696	7	232.91	KBTBD1	Marbling score
C	7	22993178-23001567	6	83.89	-	Inflammatory response
C	8	24844168-25057656	5	213.49	KIAA1797	Somatic cell and marbling score
A	10	70455224-70552388	6	97.16	BMP4	Carcass trait, Udder Depth, Milking yield
B	13	78430096-78793499	9	363.43	KCNB1	Body weight (slaughter), weaning weight, teat length
B & C	14	46833665-46838453	6	47.88	FABP4	Intramuscular and subcutaneous fat deposition
B	16	45425579-45874444	8	448.87	AJAP1	Carcass weight, bone percentage, calving ease
B & C	16	70812261-71003746	7	191.49	HSD11B1	Residual feed intake, body weight (weaning and birth)
B	18	44880710-45044933	6	164.23	GUCY2D	Gastrointestinal nematode burden
B & C	20	31890736-32064270	6	173.54	GHR	Intramuscular and subcutaneous fat deposition
A	24	34248516-34415731	5	167.22	RBBP8	Udder depth, interval to first estrus after calving,

*Group; Group A- Achi, Bhagnari, Cholistani, Dhanni, Dajal, Kankaraj, Red Sindhi, Sahiwal), Group B- Lohani and Group C-Tharparkar; Chr-Chromosome.

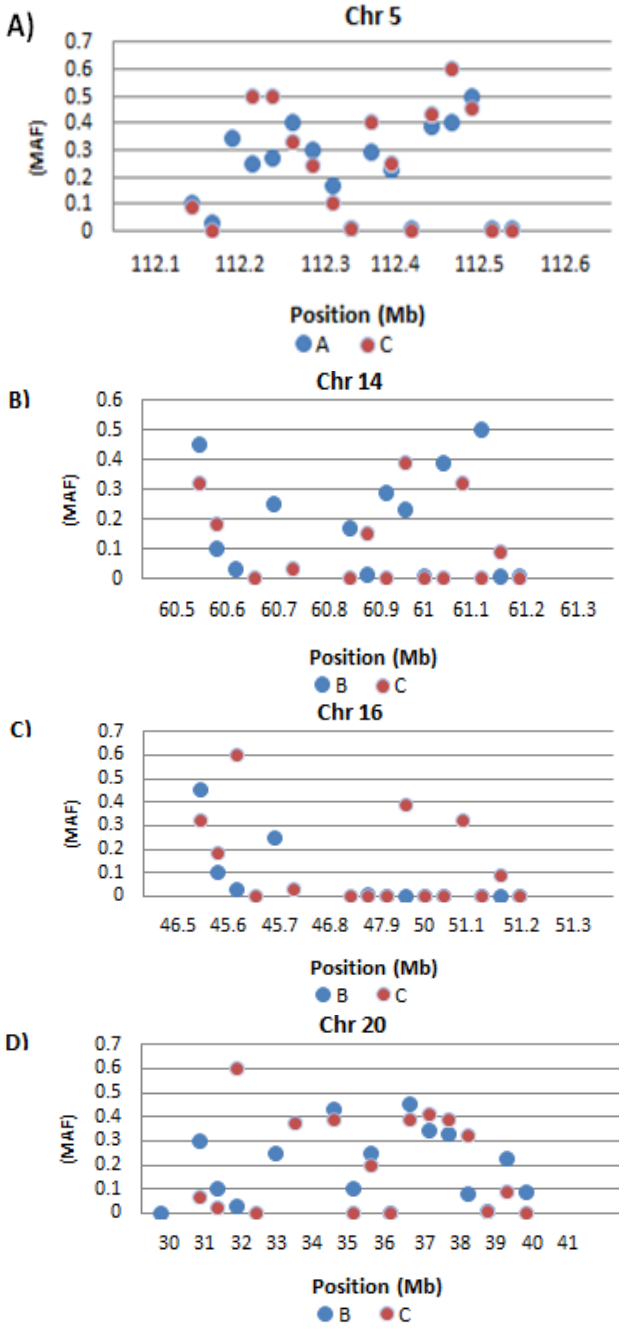

Fig. 1: Selective sweep regions shared between two Groups. (A) A and C (B) B and C (C) B and C, (D) B and C, Chr = Chromosome.

The most intensive differentiated genomic portion was observed between A vs. B & C pair on BTA -16 between 49, 386, 191-49, 867, 758 bp. Comparison of population A vs. B & C; B vs. others and C vs. others suggested a differentiated genomic region on BTA -06 between 38, 840, 864-38, 992, 112 bp that was common across all three populations.

Annotation of genome region: To identify potentially expressed genes, forty-nine reference sequences were annotated using analyzed candidate regions obtained from both within and between populations. Some candidate gene sequence varied from 1-8, that were obtained across the genome and numerous contender genes connected with main biological functions and their consequent pathways in these populations using the PANTHER web portal (Mi *et al*., 2013). These regions include MC1R and GUCY2D on BTA 18 between 14, 757, 332-14, 759, 082 bp was found under selection in these three populations (A, B and C) that was previously studied in some tropical *Bos indicus* cattle breeds (Stella *et al*., 2010). Other regions were associated with production trait, including, FABP3, BMP4 (A), HOXC13 (A and C), RPS6KA2 (B), FABP4 (B and C), LEPR, SAR1B (C), LAP3, CAPN3 (A, B and C), reproduction traits KBTBD1, KIAA1797, PIK3CA (C), SPERT (B), IGF1R (A and C), nervous system MC1R (A, B and C) KIT, ASIP (B and C), FGF5, HSPB9 (B) and immune system SERPINA3-8 (A, B and C), BOLA3 (B and C), IL4 (C) and IL2 (B). Candidate genes MYO6, PREP, NPR2, MTPN, DNAJC16 and NCAPG related to growth, metabolic processes and skeletal development were also identified that are under selection. Candidate gene MC1R on chromosome 18 between 14,757, 332-14, 759, 082 bp were identified in these selected breeds (Sophie *et al*., 2013). All selected candidate genomic regions were examined to investigate either these candidate regions overlap with any previous reported QTLs in cattle breeds or not. Thus, we used online published Bovine QTL catalog and discovered that most of the candidate genomic regions overlap with these reported regions. These regions harbored QTLs that affect production, reproduction, nervous system and immune system related traits. Therefore, in this study, we compared ten candidate selection signatures with some previous reported bovine selective sweeps, which clearly support these harbor variants with huge phenotypic effects in these populations.

DISCUSSION

In this study, we used two different methods to find out candidate selection signatures, which might have an impact on variation within the genome of cattle breeds. First, we detected comprehensive selective sweeps through long haplotypes fixation within these three populations, which was similar to as reported by Ramey *et al*. (2013). It has been reported that long homozygous haplotypes were not added in Bovine chip design and might be created by chance due to SNP ascertainment bias and this may lead to produce a low minor allele frequency (MAFs) in some cattle breeds. To declare a selective sweep, we required number of loci to secure ascertainment bias effect, where "N" was defined for each breed individually. Secondly, we identified genomic regions using population differentiation index (Fst) method, among the three population combinations (A, B and C) using sliding windows across the entire genome and exposed differentiation, which might be possible to be produced from different selection centers and adaptation history of production traits in their respective local environmental condition (Helyar *et al*., 2011). Population differentiation index (Fst) method can identify different kinds of signature selection at population level either this differentiation due to any drift and two methods of selection signatures did not produce overlapping signals in the same data set.

In this study we identified fifty-three contender genome regions, which are possible under selection historically. Twenty candidate genome regions were identified within these three populations and twenty- five were detected as diverged between breeds. A considerable attributes have been occurred in the shape of animal morphology and behavior during the domestication event. Coat color of animals is an easily identifiable phenotype and historically this trait was most promptly used for breeding for future selection (Andersson and Georges, 2004). In Pakistan, different coat color patterns are well recognized as breed characteristics. However, color in sub-tropic cattle breeds may be considered as an adaptability trait (Malkina *et al*., 2015). The coat color pigmentation is controlled by melanocyte stimulating hormone receptor (MCIR) gene, situated on BTA-18; 14, 757, 332-14, 759, 082 bp and stimulate the production of pheamelanin and eumelanin pigments (Seo *et al*., 2007). In this study, we found no differentiation among these three populations for MCIR gene. This suggests that specific alleles at MCIR may be under selected in these breeds. MCIR gene was already reported under selected in some previous studies of different cattle breeds (Ramey *et al*., 2013; Malkina *et al*., 2015). The existence of candidate signature of selection on MCIR in all these breeds, characterized by multi-coat colors that may exist in many forms (white, gray, brown, spotted, black color pattern), is an important indicator which has been already studied in Hanwoo and south African cattle breeds (Ramey *et al*., 2013; Malkina *et al*., 2015).

MacHugh *et al*. (1997) studied the behavioral traits in some cattle breeds and suggested that during domestication process sociability character was increased and at the same time fear and anti-predator responses were reduced. In this study, we identified some signatures of selection that may be related to behavior characteristics, especially with respect to the growth of the nervous system and regulate the tissue functions. These regions include DNAJC16 (A, B and C) on chromosome 16. These signatures of selection, associated with the nervous system are also reported in some African Zebu and Sanga cattle breeds (Malkina *et al*., 2015).

Bos indicus breeds of the South Asian region, especially Pakistani indigenous cattle breeds are well adapted to scarcity and harsh environmental conditions (feed shortage), and highly resistant to internal and external parasites (Mustafa *et al*., 2014). This study has detected candidates of tropical adapted genes signals in Lohani cattle, which are also reported in many studies, in some other Zebu breeds (Sophie *et al*., 2013). These include MCIR gene and HSPB9 on chromosome 19 between 14757332-14759082 and 42896570-42897840 bp and conferring that Heat shock proteins are extremely linked to adaptation traits for the tropical environment in indicine population, therefore, expressed differentially between *Bos indicus* and *Bos taurus* in tropical condition (Gibbs *et al*., 2009; Chan *et al*., 2014). In tropical condition, the coat color and hair thickness influence the thermal resistance in cattle (Muchenje *et al*., 2008). However, lack of keratins and heat shock protein signals were observed in other cattle breeds (name those breeds here) in this study, which are also habitant of similar environments. Intermediate allele frequencies of keratins and HSB9 loci may have under selection in these breeds, which has been already reported in some African zebu breeds (Malkina *et al*., 2015).

The candidate genes for the development of immune system detected in this study were related to antigen recognition, which mediate the immune response. These genes include MTPN, KCNBI (Lohani and Tharparkar) BTA 4;-13, CYM, NDUFA12, SLC25A48 (Tharparkar) BTA 3, -7, CDC6, TNS4, ALOX15B, ALOX12B (Lohani) BTA 19 and CDK10 (all breeds) BTA 18. Zhang *et al*., (2011) reported TNFAIP8L2 gene to be related with immune homeostasis and NDUFA12 gene divergent allele frequency between *Bos indicus* and *Bos taurus* cattle, which is linked with tick resistance. The observations of CD family of candidate genes in Pakistani indigenous cattle breeds are consistent with the resistant to internal and external parasites. Additionally, identified putative genomic regions overlap with previously detected QTL include MTPN (Lohani and Tharparkar), PDPN, DNAH2, TMEM88, GUCY2D (all breeds), DCC, EBF1, CXCL14, SLC25A48 (Tharparkar) and OTX2 (Group A and Tharparkar) gene, which are reported as affected for internal and external parasite tolerance in different cattle breeds.

Some candidate genomic regions are considered directly or indirectly related with the reproductive pathways, including testicular development, spermatogenesis, estrus cycle, ovulation rate etc. in cattle (Stella *et al*., 2010; Gurgul *et al*., 2016). These putative regions include OVOS2, ADIPOR2, WC1, HOXC12, HOXC13, FBXL14 (Lohani and Tharparkar), RBBP8 (Tharparkar) and SERPINA3-8 (Group A and Tharparkar). These indigenous cattle breeds are well adapted to reproduce under harsh climatic conditions and are an excellent source of dam lines, with little calving

difficulties, for crossbreeding programs (Malkina *et al.*, 2015). These phenotypes characteristic supports the occurrence of positive signals at different loci, which probably are associated with reproduction and there is strong evidence that these traits were developed during the adaptation in Pakistani climatic conditions. Interestingly, these putative genomic regions for reproductive traits overlap with previously detected QTLs.

Growth traits are considered to be of high value in the beef breeds. In this study, under selection of some putative growth traits were identified. Candidate regions included DDX19A, TMEM51, AJAP1 (all breeds) BTA 18, -16, MTPN, KCNB1, MYO6 (Lohani and Tharparkar) BTA 13, 9, IGFBP4 (Lohani) BTA 19, TGFB1, KIAA1797 and ATOX1 (Tharparkar) BTA 7, -8. These regions overlap with previously detected QTLs which are linked to body weight, growth rate, stature, wither height, body length etc. Some overlap with previously reported QTLs for milk production traits, including milk yield, SNF (BTA 3, 5, 10, and 16), feed efficacy traits (BTA 13, 16, 18) and marbling score carcass traits. This study established 12 detected putative genomic regions which were common among these three cattle populations and some of these overlapped with previous QTL studies (Malkina *et al.*, 2015). This study attempted a more comprehensive genomic picture across the indigenous cattle breeds for traits of economic importance, especially the adaptability characteristics and parasitic resistance to enhance the productivity and reproductive efficiency in Pakistan.

Conclusions: There appears to be under selection of some genomic regions with reference to adaptability and production traits of Pakistani cattle breeds. Regions were identified that appears to be associated with adaptability characters, immune response, parasitic resistance, and productivity and reproductive traits. Some of these regions overlap with some previously reported QTLs that might be used effectively for animal`s selection.

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Authors contribution: HM, TSS, and WAK conceived and designed the study. HM, AA, KE, ZHK, MTJ executed the experiment and analyzed data. All authors interpreted the data, critically revised the manuscript for important intellectual contents and approved the final version.

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