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Genomic Signatures of Positive Selection and Local Adaptation in Ethiopian Sheep Populations

B. E. Demissie[a,b,*], G. M. Tarekegn[c,*], H. Dadi[a,d], Z. Edea[d], A. A. Woldesemayat[a], K-S Kim[e], S. Girma[f], T. Seyoum[f], K. Melaku[f], & S. Keskes[a,*]

[a]Department of Biotechnology, Addis Ababa Science and Technology University, P. O. Box 16417, Addis Ababa, Ethiopia
[b]Department of Animal Science, Haramaya University, P.O. Box 138 Dire Dawa, Ethiopia
[c]Scotland's Rural College, Roslin Institute Building, University of Edinburgh UK
[d]Bio and Emerging Technology Institute, P. O. Box 2490, Addis Ababa, Ethiopia
[e]Department of Animal Science, Chungbuk National University, Cheongju, Chungbuk 361-763, South Korea
[f]Armauer Hansen Research Institute, P.O. Box 1005, Addis Ababa, Ethiopia
*Corresponding authors: simenew.melaku@gmail.com; belayeng4@gmail.com
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ABSTRACT

Domestic sheep (*Ovis aries*) have adapted to diverse ecological regions and exhibit various phenotypic traits through long-term natural and artificial selection. Indigenous sheep populations, in particular, have developed valuable traits such as disease resistance, heat tolerance, and resilience to harsh environments. Understanding the genetic mechanisms underlying these adaptive traits is crucial for enhancing, sustainably utilizing, and conserving sheep genetic resources. In this study, we aimed to assess genomic selection among five Ethiopian indigenous sheep populations sampled from various ecological regions. Whole blood samples were randomly collected from 48 sheep representing two populations (Semien and Selale) from different ecological regions and genotyped using the Ovine 50K SNP BeadChip. Genotype data from three Ethiopian sheep populations was additionally included in the analyses. Fixation index (F_{ST}) and cross-population extended haplotype homozygosity (XPEHH) methods were used to detect signatures of positive selection. Functional analysis revealed genes related to plateau adaptation, immune response, and tail fat formation. Our study identified potential genes associated with alpine and sub-alpine adaptation, including *GABRG3*, *SYT1*, *TGFBR3*, *ITPR2*, *KCNMB2*, and *ATP1A3*. Candidate genes linked with wet highland adaptation, including *GNB1*, *HDAC9*, *IGFBP6*, *JAKMIP1*, *PAK2*, and *EXOC4*, were also detected as under selection. The BMP2 gene, known for its fundamental role in sheep adipose tissue, emerged as a positional candidate gene for tail fat formation. This study offers novel insight into genomic adaptation to alpine, sub-alpine, and wet highland ecological regions in sheep and provides a valuable resource for further investigation. Moreover, it contributes worthwhile information for sustainable conservation and utilization, and lays the groundwork for future research into the genetic mechanisms behind sheep adaptability to diverse ecological regions.

Keywords: adaptation; candidate genes; indigenous sheep; putative regions; selection signatures

INTRODUCTION

The key factor in modern agriculture is the ability of livestock breeds to adapt to local climates, which reduces stress on animals and fosters environmentally sustainable production (Berman, 2011). Sheep are among the earliest domesticated livestock species, dating back approximately 10,500 years in the Fertile Crescent region (the Iranian Zagros Mountains and Southeastern Anatolia) (Alberto *et al.*, 2018; Demirci *et al.*, 2013). African sheep were likely domesticated in the Near East before being introduced to the continent via the north (both thin- and fat-tailed sheep) and the Horn of Africa (fat-tailed sheep) (Muigai & Hanotte, 2013). Since their arrival, sheep have accompanied humans to various and often extreme environments, including high altitudes, cold, and hot climates. Globally, approximately 1,000 sheep breeds (Ovis aries) have adapted to diverse environmental conditions, making them a valuable model for studying genetic adaptation. Domestic sheep's broad agronomic and adaptive traits, along with significant genomic variation across both improved and local breeds, reflect their global dispersal and adaptation under varied environmental and production systems (Bettencourt *et al.*, 2015; Cao *et al.*, 2021; Li *et al.*, 2020). Small ruminants, particularly native breed kinds, play a significant role in the livelihoods of a considerable part of the human population in the tropics from socio-economic aspects (Ahmadabadi *et al.*, 2023). Thus, combined trials with emphasis on administration and genetic progress to improve animal outputs are of decisive significance

(Saadatabadi *et al.*, 2023). Economical and biological efficiency of small ruminant production enterprises generally improves by increasing the productivity and reproductive performance of these animals (Mohammadabadi *et al.*, 2024).

In Ethiopia, the livestock sector is a cornerstone of family farms and the national economy (FAO, 2018). Sheep play a significant role, with nearly one-third of smallholder farmers raising them for diverse products such as meat, milk, skin, and manure (Negassa & MJabbar, 2008). Sheep are particularly valued for their low cost, suitability for care by women and children, and resilience in marginal environments, making them a focus of community-based breeding programs (Haile *et al.*, 2013). Ethiopia has been a key entry point for cattle and sheep from the Middle East, and today, it boasts high genetic diversity in native livestock species (Edea *et al.*, 2017; Muigai & Hanotte, 2013). The significant genetic and phenotypic variation among Ethiopian sheep populations across diverse ecosystems provides an ideal setting for studying environmental adaptation (Ahbara *et al.*, 2019; Edea *et al.*, 2017; Gizaw *et al.*, 2007).

Adaptation in livestock, including sheep, is driven by natural selection, while artificial selection has been instrumental in enhancing desirable traits for agriculture (Brito *et al.*, 2017). Along their expanding paths, sheep have thrived in a wide range of environmental conditions due to centuries of selection that have resulted in local adaptation (Liu *et al.*, 2016). Tail fat deposits, for instance, provide energy reserves that enable sheep to survive under harsh conditions, such as prolonged droughts, cold, and food scarcity (Moradi *et al.*, 2012; Nejati-Javaremi *et al.*, 2007). As described by (Kalds *et al.*, 2021), sheep exhibit five distinct tail phenotypes based on fat deposits: the long fat tail, short fat tail, fat-rumped, long thin tail, and short thin tail. These phenotypes are represented in African indigenous sheep populations, with fat-tailed sheep common in Northeast, East, and Southern Africa, thin-tailed sheep primarily in Northwest and Western Africa, and fat-rumped sheep limited to the Horn of Africa (Porter, 2020). Archaeological evidence suggests that thin-tailed sheep, likely the earliest type on the continent, were introduced through the Levant via the Suez Canal and the Horn of Africa (Gautier, 2006; Marshall, 2000). Rock art from the Lake Turkana region (4,500–3,500 BP) shows thin-tailed sheep, which are now mainly found in Ethiopia (Benishangul-Gumz and North Gondar regions), Sudan, and West Africa (Barthelme, 1985; MacDonald & MacDonald, 2006).

Several approaches have been used to identify candidate regions and genes associated with tail fat deposition and local adaptation in sheep breeds. Copy number variations intersecting key genes (PPARA, RXRA, and KLF11) related to fat deposition have been identified in three Chinese sheep breeds: Large-tail Han, Altay, and Tibetan (Zhu *et al.*, 2016). Other genes, such as BMP2 and VRTN, have been associated with fat-tail characteristics in Laticauda and Cyprus fat-tail breeds, as well as 13 Italian thin-tail breeds (Moioli *et al.*, 2015). Several putative candidate regions spanning genes influencing growth traits and fat deposition, such as NPR2, HINT2, SPAG8, and INSR, along with genes involved in limb and skeletal development and tail formation, including ALX4, HOXB13, and BMP4, were identified in the study conducted on 11 Ethiopia indigenous sheep populations (Ahbara *et al.*, 2019). Despite Ethiopia's diverse landscapes and sheep populations adapted to high- and low-altitude regions, limited studies have explored genes and pathways linked to ecological adaptation and phenotypic variation. Genes related to altitude adaptation (MITF, FGF5, MTOR, TRHDE, and TUBB3) have been identified in five Ethiopian sheep populations (Edea *et al.*, 2019). However, several indigenous Ethiopian sheep populations, such as the Semien and Selale, have yet to be thoroughly studied for ecological adaptation, and genes that may be associated with ecological adaptation and phenotypic variation need to be identified. This study aims to detect selection signatures within the genomes of Ethiopian indigenous sheep using medium-density SNP genotype data, enhancing our understanding of their adaptability and potential for sustainable breeding programs.

MATERIALS AND METHODS

Ethical Approval

The study protocol was approved by the Institutional Animal Care and Use Committee (IACUC) (Approval No: DLW-ARO/2022-16).

Sample Collection and DNA Extraction

Blood samples were collected from 48 mature animals of both sexes, randomly sampled from multiple flocks of Selale (n= 24) and Semien (n= 24), sheep populations adapted to distinct ecological regions (Table 1). Blood samples were collected from the jugular vein using a 5 ml vacutainer tube containing 1 ml EDTA as an anticoagulant. The samples were refrigerated at -20 ^{o}C until DNA isolation. DNA was extracted using the QIAamp® DNA Mini kit following the procedures for blood or body fluids (vacuum protocol). The NanoDrop spectrophotometer and 1 % agarose gel electrophoresis were used to measure the concentration and purity of DNA.

Besides, genotype data of 36 animals representing three Ethiopian sheep populations, including Blackhead Somali (n= 14), Horro (n= 10), and Menz (n= 12), were used to detect signals of ecological adaptation. The genotype data were obtained from the NRSP-8 Community File Sharing Platform (https://www.animalgenome.org/repository/pub/KORE2017.1122/).

Genotyping and Quality Control

A total of 48 animals were genotyped using the Ovine 50K SNP BeadChip at TNT Research Co., Ltd., South Korea. Genotype data from both the 50K and 600K SNP BeadChip platforms were combined using PLINK v1.9 (Purcell *et al.*, 2007), and 35,249 SNPs were identified as overlapping between the two chips.

Table1. Phenotypic characteristics and ecological variables of the study sheep populations

Sheep populations	Coat color	Fiber type	Tail type	Horn	Agro-ecology	Altitude (m)	Management	Purpose of keeping sheep
Selale	Brown, White, Red	Short-haired	Long fat-tail	Male horned, most females polled	Wet highland	1500 -2700	Mixed crop livestock	Meat
Semien	Brown, White, Black	Short-haired	Short fat tail	Males horned and short horns in most females	Alpine mountains	3000- 4000	Mixed crop livestock	Meat
Horro	Brown, fawn	Short-haired	Long fat-tail	Polled	Wet highland	1400–2000	Mixed crop livestock	Meat
Menz	Black, Brown, white	Coarse wool	Short fat-tail	Horned	Sub-alpine	2500–3000	Sheep-barley	Meat & Wool
Blackhead Somal	White body, black head and neck	Short-haired	Short fat rump	Polled	Arid lowland	500–1500	Pastoral/agro pastoral	Meat

Source: (Edea *et al*., 2017; Gizaw *et al*., 2008; Abera *et al*., 2014)

Autosomal SNPs with call rates below 95% and Minor Allele Frequencies (MAF) less than 0.05 were filtered out using the software mentioned above. Following quality control procedures, 35,139 SNPs remained for downstream analyses.

Genetic Population Structure

Principal Component Analysis (PCA) was conducted in PLINK v1.9 (Purcell *et al*., 2007) to examine genetic structure and relationships among the populations based on genetic correlations. The first two Principal Components (PC1 and PC2) were visualized using the ggplot2 package in R (Wickham, 2009). Admixture analysis was performed using ADMIXTURE v1.3.0 (Alexander *et al*., 2009) to estimate the proportion of shared genome ancestries and to investigate genetic structure within the populations. A 5-fold cross-validation procedure (Alexander & Lange, 2011) was applied to determine the optimum number of ancestral populations (K), providing insights into genome ancestry proportions shared among populations.

Detection of Genomic Regions and Genes Under Selection

Based on PCA results, we performed two separate analyses: one between alpine and sub-alpine sheep populations (Menz and Semien) versus arid lowland (Blackhead Somali), and the other between wet highland (Selale and Horro) versus arid lowland (Blackhead Somali) populations. We applied two complementary statistical tests to identify selection signatures: Fixation index (FST) and cross-population extended haplotype homozygosity (XPEHH). FST and XPEHH are particularly effective in identifying complete or nearly complete selection signals. Given the extended time necessary for fixation, these methods are generally expected to detect older selection events across populations, with FST being especially adept at uncovering evidence of selection from more distant historical periods (Cadzow *et al*., 2014). FST values, computed according to (Weir & Cockerham, 1984) in PLINK v1.9 (Purcell *et al*., 2007), were used to identify the top 1% of loci with high differentiation as candidate regions under selection. The XPEHH test (Tang *et al*., 2007), designed to detect SNPs under selection in one population but not in another, was used to perform a complete selective scan. This test compares haplotype homozygosity (EHH) and integrated Haplotype Score (iHS) among populations, identifying distinct SNPs in homozygous states for one population and polymorphic for others. The XPEHH statistic was calculated as follows:

XPEHH=In (IA/IB),

where IA is the integrated EHH value for the test population, and IB is the integrated EHH value for the reference population.

A positive XPEHH value indicates selection in the test population, while a negative value indicates selection in the reference population. XPEHH scores for each locus were calculated using the *rehh* package (M. Gautier & Vitalis, 2012) in R, and scores were standardized for visualization and interpretation of regions under selection.

Annotation of SNPs Under Selection

SNPs showing significant differentiation in the FST and XPEHH analyses were annotated using Ensembl Biomart (https://www.ensembl.org/index; accessed on 16 March 2024) with the ARS-US_Ramb_v2.0 ovine reference genome. Only significant SNPs were retained to ensure confidence in identifying outlier SNPs within genomic regions under selection.

Functional Enrichment Analysis of Candidate Genes

Gene enrichment analyses were performed using the Database for Annotation, Visualization, and Integrated Discovery (DAVID; https://davidbioinformatics.nih.gov/; accessed on 16 March 2024) (Huang *et al*., 2009). Fisher's exact test (P= 0.05) was applied to identify significantly enriched Gene Ontology (GO) categories, including biological process, molecular function, and cellular component classifications. KEGG pathway enrichment analysis identified significantly enriched metabolic or signal transduction pathways associated with candidate genes.

The criteria for determining significantly enriched pathways matched those used in the GO analysis.

RESULTS

Genetic Population Structure and Admixture

Principal component analysis (PCA) was performed to visualize genetic relations within individuals and between the five Ethiopian indigenous sheep populations. The first two (PC 1 and 2) principal components, explaining 20.64% of the total differentiation, were used to illustrate the relationship among Ethiopian indigenous sheep populations (Figure 1). It is indicated that the first component explained 10.78% of the genetic variability and clustered the target breeds according to topographical origin. Accordingly, Blackhead Somali (BHS) sheep populations are separated from the rest of the populations, and Selale and Horro sheep populations tend to cluster together.

For ADMIXTURE analysis, the dataset was tested by one to sixteen hypothetical ancestral clusters (K). The cross-validation error suggested K= 3 as the optimum number of ancestry proportions (Figure 2). Menz and Semien sheep populations dominate Cluster 3, sharing slightly with the BHS sheep population (Figure 3). The close clustering observed between Ethiopian native sheep populations Selale and Horro might be because of their tail phenotype (long fat-tailed) on top of their similar ecological region. The admixture result showed a substantial genomic share of Semien and Menz sheep populations, indicating their common ancestry.

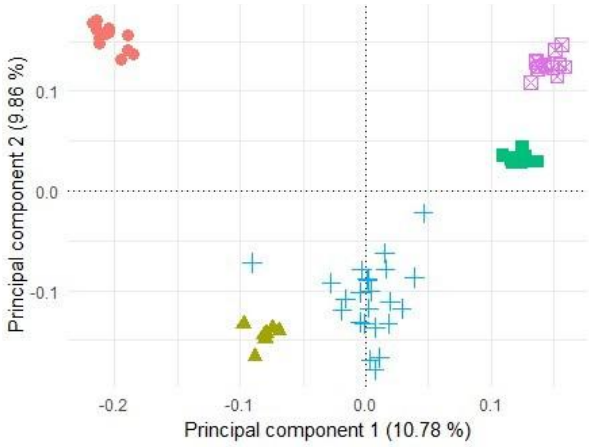

Figure 1. Principal component analysis plot of the study sheep populations based on the top two principal components with different colors representing the populations. Sheep breeds: ●, BHS; ▲, Horro; ■, Menz; +, Selale; ⊠, Semien.

Detection of Genome-Wide Selection Signatures

In the current study, we calculated the genome-wide distribution of the F_{ST} and XPEHH values to uncover selection sweeps associated with adaptive traits between the groups of sheep populations from alpine and sub-alpine (Semien and Menz) and wet highland (Selale and Horro) ecological regions. A sheep population from arid lowland (Blackhead Somali) was selected as a reference group to identify candidate genes related to ecological adaptations.

In pairwise comparisons of alpine and sub-alpine (Semien and Menz) populations and against Blackhead Somali sheep, a total of 109 candidate genes across 26 autosomes were identified using the F_{ST} selectin scan method (Figure 4). The strongest candidate regions were mapped on chromosomes OAR3, OAR6, OAR2, OAR16, OAR13, OAR14, OAR15, OAR18, and OAR5, which

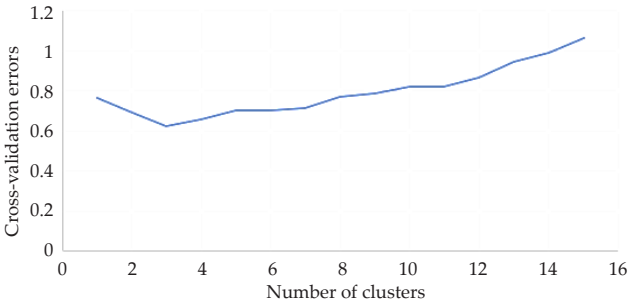

Figure 2. Cross-validation errors calculated for hypothetical ancestral clusters (K) values ranging from one to sixteen

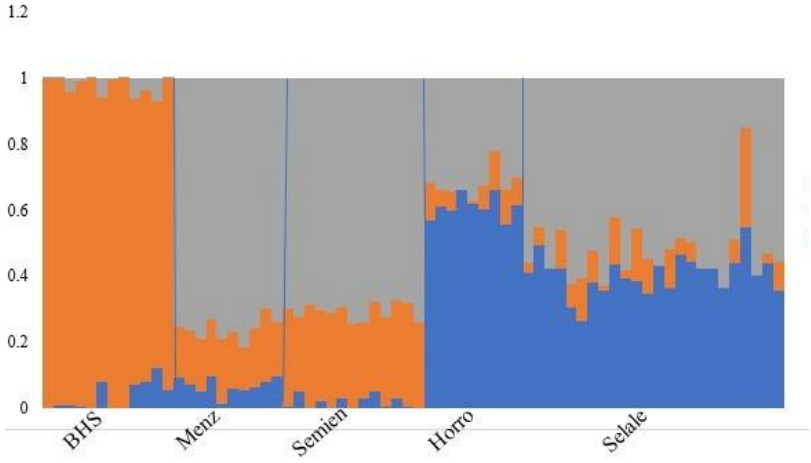

Figure 3. Analysis of population structure by ADMIXTURE. The x-axis indicates the study sheep populations and cluster membership of each population is displayed on the y-axis. The color coding (P1=blue, P2=orange, P3=gray) indicates the dispersion of the populations to distinct clusters.

spanned multiples genes such as *OSR1, SYT1, PAWR, IGFBP6, ARID2, JAKMIP1, ARHGEF19, DNAH7, ASTN2, GALNT13, LPCAT1, ADAMTS12, DOCK2, BMP2, ATP1A3, RPGRIP1L, CBLC, GABRG3, ERCC1, SORL1,* and *PTPRS* (Table 2).

The XPEHH analysis was also performed to reveal genomic regions under selection. A total of 43 candidate genes across 26 autosomes were detected by the XPEHH selection scan methods (Figure 5). Accordingly, the strongest candidate genomic regions were located on OAR3, OAR18, OAR5, OAR5, OAR22, and OAR13, and covered multiple genes, for instance, TSPAN19, SYT1, ITPR2, GLIPR1L2, ELMOD3, PLXNC1, ANKS1B, AGBL1, GABRG3, GABRA5, TENM2, MCTP1, ATP1A3, SPINK5, FARSA, CFAP58, and CFAP61 (Table 2).

Gene functional enrichment analysis was computed by DAVID software for the combination of genes identified using both F_{ST} and XPEHH selection scan (identification of positive selection) methods. The functional annotation of genes from the intersected regions generated significant ($p<0.05$) Gene Ontology, and Kyoto Encyclopedia of Genes and Genomes (KEGG) pathways were enriched (Table 3).

For the comparison between the wet highland sheep populations (Selale and Horro) and the Blackhead Somali sheep population from the arid lowlands, multiple genomic regions with high F_{ST} values were observed. We designated the top 1% of genomic regions as candidates under selection, and 111 candidate genes were detected (Figure 6). The strongest candidate genomic regions were located on OAR4, OAR11, OAR6, OAR3, OAR1, OAR5, OAR12, and OAR2, and spanned multiple genes, including *HDAC9, TWIST1, EXOC4, CHCHD3, TOP2A, IGFBP4, KRT24, NELFA, ADGRL3, MAD2L1, JAKMIP1, PAWR, LMX1A, MEGF10, ASTN1,* and *ARHGEF19* (Table 2).

We also performed the XPEHH to reveal genomic regions under selection to compare the wet highlands

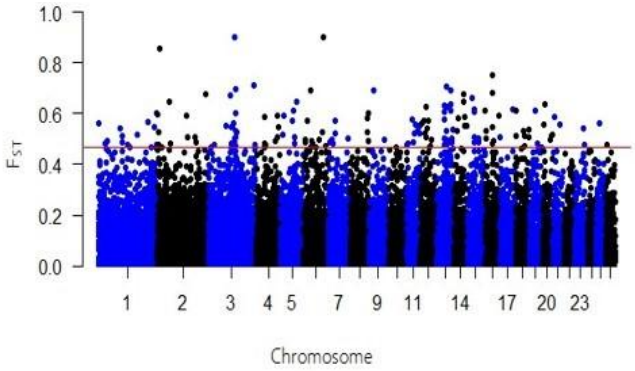

Figure 4. Manhattan plots of selection signatures determined by comparing the alpine and sub-alpine sheep populations with arid lowland sheep populations using the F_{ST} approach. The two colors, blue and black, are used solely to distinguish each chromosome clearly.

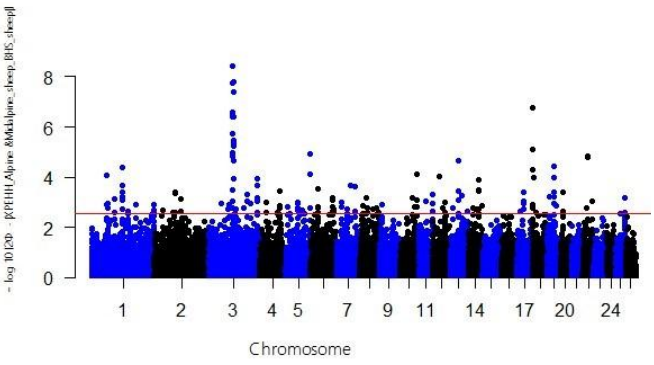

Figure 5. Manhattan plot of selection signatures determined by comparing the alpine and sub-alpine sheep populations with arid lowland sheep population using the XPEHH approach. The two colors, blue and black, are used solely to distinguish each chromosome clearly.

Table 2. Candidate genes putatively selected for ecological adaptations of Ethiopian sheep populations using two selection scan methods (F_{ST} and XPEHH)

Groups	Methods	OAR	Ensemble ID	Gene	Summarized Gene Function	References
Semien and Menz vs Blackhead Somali	F_{ST}	3	ENSOARG00020002405	CTNNA2	Adaptation of plateau	(Flori *et al.*, 2019)
		3	ENSOARG00020003616	SLC38A1	Response to oxidative stress	(Oguchi *et al.*, 2012); (Ogura *et al.*, 2011).
		13	ENSOARG00020003483	BMP2	Immune response/Tail fat formation	(Ruiz-Ojeda *et al.*, 2019)
		16	ENSOARG00020014360	DOCK2	Immune response	(Chen *et al.*, 2018)
	XPEHH	3	ENSOARG00020003133	ITPR2	Adaptation to plateau	(Manalo *et al.*, 2005; Touyz *et al.*, 2018)
	Both F_{ST} and XPEHH	1	ENSOARG00020008304	TGFBR3	Plateau adaptation	(Wei *et al.*, 2016)
		1	ENSOARG00020000078	KCNMB2	Immune response	(Chen *et al.*, 2023)
		3	ENSOARG00020005626	SYT1	Immune response	(Tejero *et al.*, 2016)
		14	ENSOARG00020021250	ATP1A3	Adaptation to plateau	(Mariadassou *et al.*, 2020)
		18	ENSOARG00020003804	GABRG3	Adaptation to plateau	(Lyu *et al.*, 2023)
Selale and Horro vs Blackhead Somali	F_{ST}	3	ENSOARG00020008241	IGFBP6	Immune response	(Liso *et al.*, 2018)
		6	ENSOARG00020023163	JAKMIP1	Adaptation to plateau	(Xu *et al.*, 2016)
		12	ENSOARG00020008685	GNB1	Adaptation to plateau	(Chi *et al.*, 2017)
		4	ENSOARG00020002586	HDAC9	Immune response	(Haberland *et al.*, 2007)
		1	ENSOARG00020002289	PAK2	Immune response	(Phee *et al.*, 2014)
	Both F_{ST} and XPEHH	18	ENSOARG00020003804	GABRG3	Adaptation to plateau	(Lyu *et al.*, 2023)
		3	ENSOARG00020005626	SYT1	Immune response	(Tejero *et al.*, 2016)
		4	ENSOARG00020001034	EXOC4	Immune response	(Fujimoto *et al.*, 2019)

(Selale and Horro) and Blackhead Somali sheep populations. A total of 30 genes across 26 autosomes were identified (Figure 7). The strongest candidate regions were mapped on chromosomes OAR3, OAR10, OAR2, OAR8, OAR22, OAR18, and OAR1, and covered multiple genes such as *SYT1, PAWR, CNTN1, ASXL2, KLHL1, UGGT2, GULP1, EBF2, CALCRL, SPAG16, CERKL, SCN9A, CFAP95, STK39, SPAG16, PDE7B, MXI1, GABRG3*, and *GSK3B* (Table 2).

Functional enrichment analysis was carried out for the genes identified using F_{ST} and XPEHH approaches. Significantly ($p<0.05$) enriched GOTERMS and KEGG pathways were also computed and identified (Table 4).

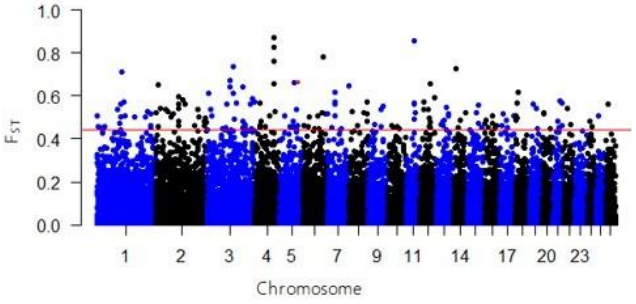

Figure 6. Manhattan plot of selection signatures determined by comparing the wet highland with arid lowland sheep population using F_{ST} approach. The two colors, blue and black, are used solely to distinguish each chromosome clearly.

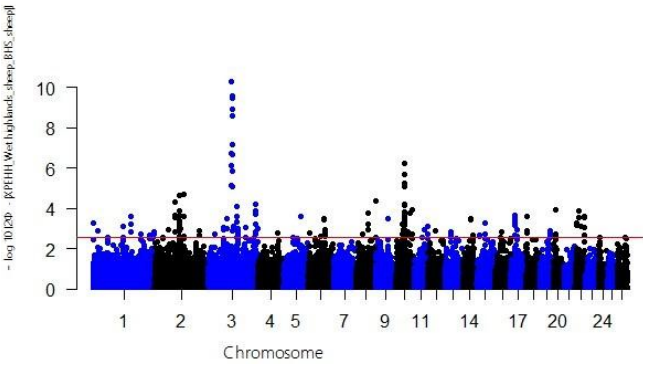

Figure 7. Manhattan plot of selection signatures determined by comparing the wet highland sheep populations with arid lowland sheep population using XPEHH approach. The two colors, blue and black, are used solely to distinguish each chromosome clearly.

DISCUSSION

The identification of selection signatures has significantly advanced our understanding of the genetic basis for important economic and adaptive traits (Tang *et al.*, 2005). These selection signatures are

Table 3. Top 10 significantly enriched GO functional annotation of candidate genes identified in the comparison of alpine and sub-alpine, and arid lowland sheep using FST and XPEHH selection scan approaches

Category	Term	Genes	p-value
GOTERM_MF_DIRECT	GO:0004890~GABA-A receptor activity	GABRB3, GABRA5, GABRG3, GABRB1	0.000
GOTERM_CC_DIRECT	GO:1902711~GABA-A receptor complex	GABRB3, GABRA5, GABRG3, GABRB1	0.000
GOTERM_CC_DIRECT	GO:0034707~chloride channel complex	GABRB3, GABRA5, GABRG3, GABRB1	0.001
GOTERM_MF_DIRECT	GO:0016301~kinase activity	PLXNA4, TPK1, PLXNC1, CERKL	0.002
GOTERM_CC_DIRECT	GO:0098794~postsynapse	GABRA5, GABRG3, GRK3, P2RX5	0.002
GOTERM_BP_DIRECT	GO:0034220~monoatomic ion transmembrane transport	GABRB3, GABRA5, GABRG3, GABRB1	0.004
GOTERM_BP_DIRECT	GO:0050877~nervous system process	GABRB3, GABRA5, GABRG3, GABRB1	0.004
GOTERM_BP_DIRECT	GO:0016477~cell migration	CTNNA2, ITGB8, CTNNA3, TGFBR3, DOCK2	0.011
GOTERM_CC_DIRECT	GO:0043005~neuron projection	GABRB3, GABRA5, GABRG3, GABRB1, TENM2, EPHB2	0.012
GOTERM_BP_DIRECT	GO:0007165~signal transduction	MAGI2, GABRB3, GABRA5, GABRG3, GABRB1, SRGAP3, TENM2, ANK2	0.017

Note: GO=GOTERM; GOTERM_MF= Molecular function; GOTERM_BP= Biological process; GOTERM_CC= cellular component.

Table 4. Top 10 significantly enriched GO functional annotation of candidate genes identified in the comparison of wet highland and arid lowland by FST and XPEHH selection scan approaches

Category	Term	Genes	p-value
GOTERM_MF_DIRECT	GO:1904315~transmitter-gated monoatomic ion channel activity involved in the regulation of postsynaptic membrane potential	GABRA5, GABRG3, GRIN2A, GRIK4	0.001
GOTERM_CC_DIRECT	GO:0098978~glutamatergic synapse	GSK3B, PAK2, GRIN2A, ADGRL3, CACNG3	0.002
GOTERM_CC_DIRECT	GO:0030424~axon	CNTN1, GSK3B, NTRK2, SYT1, SCN9A, ADGRL3	0.002
GOTERM_BP_DIRECT	GO:0045668~negative regulation of osteoblast differentiation	CRIM1, GSK3B, TWIST1	0.003
GOTERM_CC_DIRECT	GO:0045211~postsynaptic membrane	CNTN1, GABRA5, GABRG3, GRIN2A, GRIK4	0.004
GOTERM_CC_DIRECT	GO:0042734~presynaptic membrane	CNTN1, GRIN2A, GRIK4	0.025
GOTERM_CC_DIRECT	GO:0043235~receptor complex	IL6R, NTRK2, PTPRS, GFRA1	0.027
GOTERM_BP_DIRECT	GO:0006468~protein phosphorylation	GSK3B, PAK2, NTRK2, STK39, KSR2, ULK4, CAMK4	0.030
GOTERM_MF_DIRECT	GO:0005544~calcium-dependent phospholipid binding	CPNE4, C2CD5, SYT1	0.034
GOTERM_CC_DIRECT	GO:0098839~postsynaptic density membrane	GRIN2A, GRIK4, CACNG3	0.038

Note: GO=GOTERM; GOTERM_MF= Molecular function; GOTERM_BP= Biological process; GOTERM_CC= cellular component.

key in pinpointing differentially selected genes and genomic regions across various populations. To explore the genetic foundations of phenotypic, production, and adaptive traits in five sheep populations, we employed two methods (FST and XPEHH) to identify these signatures of selection. Evidence suggests that the detection of consistent selection signatures across multiple methods reinforces the case for selection in specific genomic regions (Hohenlohe *et al.,* 2010; Oleksyk *et al.,* 2010).

In domesticated animals, identifying positive selection signatures shaped by both artificial and natural selection can uncover advantageous mutations and biological pathways related to economically significant traits. Adaptations to high-altitude plateaus, for example, are regulated by complex mechanisms, including hypoxia-inducible factors, angiogenesis, vasodilation, and glycolytic metabolism (Yang *et al.,* 2016). FST and XPEHH results presented selection sweeps between alpine and sub-alpine (Semien and Menz) and arid lowland (BHS) sheep populations. In particular, the ITPR2 gene, associated with pathways like pancreatic and renin secretion and vascular smooth muscle contraction, contributes to cardiovascular responses to circulatory homeostasis, calcium signaling, water balance, and hypoxia adaptation (Manalo *et al.,* 2005; Touyz *et al.,* 2018). Similarly, the TGFBR3 gene, which plays a role in hypoxic adaptation, was positively selected (Wei *et al.,* 2016). The BMP2 gene on chromosome 13 is associated with collagen rebuilding, ECM degradation, fibrosis, and angiogenesis (Ruiz-Ojeda *et al.,* 2019) and may also play a vital role in adipose tissue formation in sheep, potentially contributing to tail fat development (Ahbara *et al.,* 2019; Zhao *et al.,* 2020). Sheep can withstand harsh situations such as extended droughts, cold, and food scarcity because of their fat depots, which serve as an energy reserve (Moradi *et al.,* 2012; Nejati-Javaremi *et al.,* 2007). We have also identified the CTNNA2 gene is linked to the development of the nervous system, neurological diseases, and climate adaptation (Flori *et al.,* 2019). Semien and Menz sheep have stable genetic performance in adapting to hypoxic environments, which can induce a series of adaptive genomic footprints that play an important role in the response to extreme high-altitude stress.

Further, selection sweeps on OAR 3 identified the SYT1 gene, which is essential for synaptic vesicle release and recently connected to spinal muscular atrophy (SMA) resilience (Tejero *et al.,* 2016). The gene is involved in counteracting the impaired neurotransmitter release, and ocular motor neurons may be able to maintain their connection to target muscles and ensure their functionality (Ruiz & Tabares, 2014). The DOCK2 gene is involved in immune and stress responses through monocyte extravasation and facilitates cell membrane polarization and actin cytoskeleton remodeling (Chen *et al.,* 2018). The KCNMB2 gene plays a vital role in insulin secretion regulation, influencing muscle protein synthesis and glucose metabolism (Chen *et al.,* 2023; Ding *et al.,* 2018; Urschel *et al.,* 2014). The study also identified the GABRG3 gene, associated with bone development and metabolism (Lyu *et al.,* 2023), and the ATP1A3 gene on OAR 14, which is associated with cellular energy regulation and lipid metabolism in various metabolic processes (Mariadassou *et al.,* 2020). The SLC38A1 gene on chromosome 3 encodes a glutamine transporter expressed in hair cells (Oguchi *et al.,* 2012) and is involved in oxidative stress responses (Ogura *et al.,* 2011).

Ovine chromosomes 4, 11, and 6 showed the strongest signals based on the FST method, while OAR3, OAR10, and OAR2 were prominent based on the XPEHH approach results presented for selection sweeps between wet highlands (Selale and Horro) and arid lowland (BHS) sheep populations. Noteworthy candidate genes included IGFBP6, which appears to play roles in immune system function and hyperthermic response through monocyte and T-lymphocyte chemotaxis (Liso *et al.,* 2018), GABRG3 gene involved in bone development and metabolism (Lyu *et al.,* 2023); SYT1 gene important for the release of synaptic vesicles and has recently been associated with differential vulnerability in SMA (Tejero *et al.,* 2016); and JAKMIP1, which potentially influences the balance between food intake and energy expenditure (Xu *et al.,* 2016).

Other important genes identified include the GNB1 gene, which is involved in hypoxic adaptation and light transduction pathways influenced by altitude (Chi *et al.,* 2017). The HDAC9 gene regulates immune response and muscle differentiation through the transcriptional activity of MEF2 and thus impairs the transcriptional circuitry of muscle differentiation through the negative feedback loop (Haberland *et al.,* 2007). Additionally, PAK2 on OAR 1 governs thymocyte maturation and actin cytoskeleton-dependent signaling and is involved in multiple processes of development and maturation of thymocytes (Phee *et al.,* 2014). The study also identified EXOC4 on chromosome 4, a gene associated with glucose metabolism, essential for insulin-mediated GLUT4 transport in muscle and adipose tissue (Fujimoto *et al.,* 2019). Findings suggest that attention should be paid to the Semien and Menz sheep with the possibility of using them as a source for future breeding programs focused on high-altitude adaptability, which emphasizes the conservation of indigenous populations.

CONCLUSION

Selection signature analysis identified several putative genomic areas covering genes associated with plateau adaptation, immune response, and tail fat formation. The findings provide valuable information to support the genomic enhancement of indigenous sheep populations and other livestock species toward improving their adaptive potential in the face of climate change. They also contribute to the conservation and informed utilization of indigenous sheep genetic resources, supporting sustainable breeding and management strategies. Moreover, the findings of the study provide a basis for further investigations into the mechanisms underlying sheep adaptation to various ecological regions.

CONFLICT OF INTEREST

All the authors declare no conflict of interest.

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