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GENOME-WIDE ANALYSIS REVEALS THE MOLECULAR BASIS OF GENETIC VARIATION OF IMPORTANT ECONOMIC TRAITS IN CASHMERE GOATS ON QINGHAI-TIBET PLATEAU

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ABSTRACT

Qaidam Cashmere goat is one of the few animals that can survive in the harsh environment of the Qinghai-Tibet Plateau and the adjacent alpine areas. It has a strong adaptability, thus shaping the genetic diversity of goat phenotype, morphology, physiology and other aspects. However, the molecular basis behind these genetic mechanisms remains unclear. Here, we conducted genome-wide studies of genetic variation in two different morphologies and geographical coordinates in indigenous Chinese goats to identify selective signaling in genomic regions. In the present study, we re-sequenced 10 high-altitude Chinese indigenous goat breeds and compared them with low-altitude goats. By combining θπ and Fst values, we identified 1277 overlapping selection regions that may contribute to the wool fiber traits, reproductive performance, and high-altitude adaptation of goats. Candidate genes enriched in selected regions are associated with the phenotypes in cashmere fiber traits (IGFBP3, TNF, ROCK1, WNT10B, KITLG), reproduction traits (CAMK2D, IL-18, ESR1, ANAPC13), body size (POMC), hypoxic adaptation (TH, ACER1, GNB1, HIF1A) and disease (IL-10). This study provided valuable genetic information for the basis of biological characteristics and genetic improvement of breeds.

Keywords: cashmere goat, whole-genome resequencing, adaptability, candidate genes.

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INTRODUCTION

Goats were domesticated about 10,000 years ago (Zeder *et al*. 2000).The domestication of the goat was a step forward in the history of human civilization by gradually changing natural selection into the desired direction of human beings through artificial selection. Goats provide meat, milk, and fur materials for human beings. Domestic goats retain a unique selective signature and are an important local genetic gene pool (Yue *et al*. 2017). Cashmere is a kind of unmedullated hair fiber that extends from the secondary hair follicles of the skin. It is a high-grade raw material of pure natural animal fiber. However, the relevant selection signals behind the genetic and phenotypic polymorphism mechanisms exhibited by goats under the dual selection pressures of both artificial and natural environments remain unclear.

Genome-wide analysis can identify the selective signal of dominant alleles in hypoxic environments and adaptive genetic basis(Simonson *et al*. 2010; Scheinfeldt *et al*. 2012). Wang *et al*. (2016) identified genomic regions for phenotype and high-altitude adaptation by analyzing sequencing data from eight goat breeds. Benjelloun *et al*. (2015) identified some potential adaptive variants in 44 representative indigenous goat breeds. The identification of selected signals used the strategy of detecting regions of genetic variation in duck (Zhang *et al*. 2018), pandas (Zhao *et al*. 2013), pig (Anon 2012), sheep (Lv *et al*. 2014), dog (Liu *et al*. 2018), and goat (Dong *et al*. 2015). An extensive collection of candidate genes and possible directions for trait improvement can determine the effects of selection on the genome for use in breeding.

Qaidam cashmere goats are mainly distributed in the desert, semi-desert, and mountainous steppe areas of Qinghai-Tibet Plateau in Wulan County, Haixi Region. Goats living in these areas have adaptive solid biological characteristics and can adapt to various climatic conditions, including dry, cold, and harsh environments (Liu *et al*. 2015), reflecting phenotypic and genetic evolution of adaptability to local settings. However, the genetic footprint of genomic variation in Tibetan Plateau goats after domestication on multiple traits remains further studied.

To identify the specific genomic variation sets and superior germplasm resources of goats subjected to artificial and natural selection, we sequenced ten indigenous Chaidamu cashmere goats (altitude >3,000 m). Our experimental data were analyzed with the genome sequences of nine Chengdu Brown goats downloaded from NCBI. The present study provides a basic understanding of the genetic variation corresponding to phenotypic changes. The results will provide theoretical basis for hypoxia adaptation and quality improvement of Chaidamu cashmere goats on Qinghai-Tibet Plateau.

MATERIALS AND METHODS

Ethic statement: This study was conducted in accordance with the Regulations on the Management of Laboratory Animals and was approved by the Animal Care and Use Committee of the Northwest Institute of Plateau Biology, Chinese Academy of Sciences (NWIPB2021311).

Animals and Genome sequencing: Ear tissue samples of ten Qaidam cashmere goats (CDMG) with specie-specific characteristics adapted to local environment were collected randomly in Haixi area of Qinghai Province (altitude>3,000 m).The other sequencing data of 9 Chengdu Brown goats (CDBG) were downloaded from the National Center for Biotechnology Information (altitude<1,000 m). A library with an insertion size of 500 bp was constructed after total genomic DNA was extracted (Illumina Inc., San Diego, CA, USA). Novaseq6000 (Illumina Inc., San Diego, CA, USA) NGS platform was used for sequencing (Guangzhou, China).

Variants identification and annotation: Clean reads were compared with the reference genome using the Burrows-Wheeler Aligner (BWA). Single Nucleotide Polymorphism (SNP) was detected using GATK, SNP sites were filtered, and the filtering condition was set as: MQ (RMS Mapping Quality) ≥ 25 ; QD (Variant Confidence/Quality by Depth)≥ 2.SNPs were annotated by ANNOVAR software(Kai, Li, and Hakon 2010). Break Dancer (Max1.1.2.) was used to detect chromosome structural variations in the genome (Chen *et al*. 2009). Copy number variants (CNV) were classified by CNVnator (0.3.2) (Abyzov *et al*. 2011)

Phylogenetic and population structure analysis: Next, neighbor joining method in the PHYLIP software (version 3.69) were used to construct genetic relationships between breeds (Felsenstein 1989) and the reliability of the branches was verified (bootstrap,1000 replications). GCTA program (Yang *et al*. 2011) was used for the principal component analysis. The admixture model-based software Admixture (Alexander, Novembre, and Lange 2009) K=1~10 was selected as the mixed model to estimate the population structure. Using the method of Loiselle (Loiselle *et al*. 1995) *et al* by the software of SPAGeDi (Hardy and Vekemans 2002) V1.5 calculated the kinship matrix.

Analysis of Selective Sweep Regions: A sliding window based cross approaches was used to calculate Nucleotide Diversity (Nei and Li 1979) (π) and Fst to identify genes in the selected region. The threshold was determined by top 5% and the genes in the significant and selected regions were screened. R scripts outputs all graphics. The candidate genes can be further analyzed.

RESULTS AND DISCUSSION

Analysis of Genetic Variation: We've obtained 806.63 billion raw reads. Stringent quality filtering yielded 614.35 billion clean reads. Clean reads have a Mapping rate of over 98% to the goat reference genome (**https://www.ncbi.nlm.nih.gov/assembly/GCF_001704415.1**) with a coverage of ~99.49% (Supplementary Table S1). Compared with the reference goat genome, a total of 24.39 million variation data were generated. According to the sequencing data, most SNPs (62.59%) were located in the intergenic region. The remaining SNPs were distributed upstream (0.55%) and downstream (0.57%) of open reading frames, in introns (34.51%), and exons (0.63%), respectively (Supplementary Table S2). We also observed 60,259 non-synonymous SNV and 84,818 synonymous SNV in the exon. We also observed that 60,259 non-synonymous SNPs and 84,818 synonymous SNPs were located within the exons, with a distinct non-synonymous/synonymous ratio of 0.71, similar to that in Mouflon sheep (Ji *et al*. 2016) (0.689)(Supplementary Table S2). Next, Loci with a missing rate of more than 50% were removed, Venn graph divided 28.43 million SNPs into three parts: CDMG and CDBG had 8.57 million and 1.46 million species-specific SNPs respectively, and shared 9.86 million SNPs (Fig.1). The number of SNPs in exons, introns and intergenic regions of CDBG were less than that of CDMG. Furthermore, CDMG observed higher genetic diversity (Supplementary Table S3). The observed abundance of variation was similar in other local breeds (Ai *et al*. 2015).Principal component

analysis (PCA) explained the first principal component variation separation (10.71%)(Fig.2b). The neighbor-joining tree further confirms the significant separation of the two groups. This genetic differentiation is consistent with the environmental characteristics and origin of the breeds. The grazing patterns have a substantial effect on the adaptation genetic changes of the plateau goats. In addition, although the goats' genomes are similar, they have diverged into two different branches, probably due to genetic variations that result from long-term adaptation to their respective environments (Fig.2a).

Structural variation analysis: Comprehensive and accurate detection of indel will become more critical for targeting genomic variation (Mullaney *et al*. 2010). Furthermore, Indel and SVs are important types of chromosomal structural variation and contribute significantly to candidate molecular markers (Kim *et al*. 2018).A totalof 861,995 insertions and 1,114,290 deletions were detected. 1,129,583 InDels were observed to be shared, of which 388,539 and 741,044 were specific to CDBG and CDMG respectively. Most InDels were single nucleotide deletions ranging in length from 0 to 10 bp (Fig.3a). The detection of a large number of specific gene mutations, gene recombination, chromosome variation and so on emphasizes the importance of novel variants, and can better inform future husbandry and breeding practices to mitigate the potential for future loss of gene diversity.

A total of 31,483 structure variants were obtained. There were 4,941 insertions, 16,785 deletions, 292 inversions, 7,888 chromosomal translocations, and 1,577 tandem duplications. There were 1366 and 11915 SVs specific to CDBG and CDMG (Fig.3b), respectively, with no difference in length, and CDMG apparently retained more variation. This may have increased the breed's ability to adapt to extreme natural environments. The discovery of specific and overlapping variation of InDels is of great significance. This is because the breed specific variation preserves the inherent particularity, while the overlapping may reflect the amount of variation shared between the breeds (Stafuzza *et al*. 2018).

Genome-Wide selective sweep analysis: Whole-genome was scanned to detect regions with high degrees of fixation, which are indicative of selection signatures. The fixation index (Fst) values and π ration were used to estimate pairwise genetic differentiation, the top 5% of the 1277 overlapping selective regions (Supplementary Table S4and Fig.4b) were annotated as regions of variation containing 3184 candidate genes (Supplementary Table S5and Fig.4a) associated with genetic adaptation and goat traits. Combined with the analysis results of these methods, we can find that some existing mutations or new mutations can increase the adaptability of a species to a particular environment.

It is reasonable to assume that some changes in certain genes and biological signals alter the phenotype's adaptation to the environment. Gene ontology enrichment analysis was used to analyze the biological functions of candidate genes. The analysis identified 129 biological processes that significantly enriched candidate genes in the GO term, 24 molecular functions, and 22 cellular components with a 5% FDR threshold (Supplementary Table S6). Overrepresented candidate genes were significantly enriched in any biological processes related to a neurological system process, cell surface receptor signaling pathway, signal transduction, multicellular organismal process, response to stimulus, and single-organism cellular process. The cellular components include the membrane, intrinsic component of membrane, and intermediate filament. The molecular functions were related to molecular transducer activity, signal transducer activity, and transmembrane receptor activity. These results indicate that the effect of GO terms reflects the plateau adaptation and phenotypic traits of Qaidam cashmere goats. Twelve pathways were enriched to be significantly enriched with a 5% FDR threshold (Supplementary Table S7 and Fig.5a), which belonged to cellular processes, metabolism, organismal systems, environmental information processing four major categories (Fig 5b). Therefore, the traits associated with polymorphism of species variation may be the result of interactions between some underlying polygenes.It also highlights the complexity of adaptive mutants of important genetic information and their related biological regulatory mechanisms.

Candidate genes associated with cashmere fiber traits: Based on the above enrichment analysis, candidate genes in selected regions were further screened. Selection footprints related to fiber traits were identified in the genomic regions by scanning selection signals, including IGFBP3 (ncbi_102174541), TNF (ncbi_100861232), ROCK1 (ncbi_102171022), WNT10B (ncbi_102169259), which are associated with cashmere traits. KITLG (ncbi_100860807) gene is associated with the phenotypic trait coat color. Insulin-like growth factor binding protein-3 (IGFBP3) expressed in the dermal papilla in the human hair, which plays a specific role in the local modulation of insulin-like growth factors action during the hair growth cycle (Batch, Mercuri, and Werther 1996). Later, IGFBP3 polymorphism was also found in goats(Lan *et al*. 2007) and sheep (Ali, El-Hanafy, and Salem 2009) successively, suggesting that genes may play an essential role in hair fiber growth. Liu found the B allele significantly improves their cashmere weight, fiber length, and hair length (Liu *et al*. 2012). Tumor necrosis factor (TNF) genes promoted the proliferation of skin fibroblasts and cashmere growth by activating NF-κB signaling (Jin *et al*. 2021; Jin *et al*. 2018).Rho-associated protein kinase1 (ROCK1) belongs

to the ROCK signaling pathway, which was potentially involved with cashmere fiber traits (Zonaed Siddiki *et al*. 2020). Further research demonstrates that ROCK1 plays a vital role in the blockade of function, inhibits keratinocyte terminal differentiation, and increases cell proliferation (An *et al*. 2018).The high expression level of Wnt family member 10B (Wnt10b) (Li *et al*. 2013) promoted hair matrix cell proliferation and hair stem elongation (Liu *et al*. 2021). KIT ligand (KITLG)was related to mammalian melanogenesis and was involved in coat color-forming by down-regulating its expression (Wu *et al*. 2021). However, the development of cashmere hair follicles is affected by light, nutrition, grazing, and other external environmental factors. To a large extent, epigenetic regulation, so the mechanism of cashmere fiber occurrence needs further study.

Candidate genes associated with reproduction traits: Reproductive traits controlled by multiple genes are critical economic indexes in livestock breeding programs. Interestingly, oocyte meiosis pathways might be involved in regulating ovarian follicular maturation and ovulation. Calcium/calmodulin-dependent protein kinase type II delta (CAMK2D, ncbi_102175934) gene plays an essential role in the transferase activity and phylogeny of the bovine embryo development process (Adams *et al*. 2011).While simultaneously implanting the epithelium of the reproductive tract, Interleukin-18 (IL-18, ncbi_100861190) also maintains a level of immune protection in the uterus, cervix, and vagina against potential pathogens (Qi *et al*. 2012).Menck and Gloria all found that the dominance effect (d) ($P < 0.05$) of single-nucleotide polymorphisms in the estrogen receptors 1 (ESR1, ncbi_102189484) gene was associated with the litter size as a new genetic marker (Muñoz *et al*. 2007; Mencik *et al*. 2019). In addition, the anaphase-promoting complex subunit 13(ANAPC13, ncbi_102170094) gene in this pathway is explicitly involved in oocyte maturation (Yin *et al*. 2017).

Candidate genes related body size: Small body size is a favorable phenotype to consume less energy, which may also be an essential adaptive mechanism for goats in high altitudes-environment (Yang *et al*. 2016). Compared with Boer goat adult male and female weight, Qaidam cashmere goat male and female weight was 60kg and 40kg lower, respectively. Pro-opiomelanocortin (POMC, ncbi_102182514) is thought to be a necessary prohormone that codes for many different peptides associated with economic traits, such as growth traits. Research has reported that POMC genes polymorphisms have potential effects on carcass traits and body weight (Zhang *et al*. 2009). POMC gene may be one of the candidate genes for linear longitudinal growth of animals.

Candidate genes related to the high-altitude adaptation: Cashmere goats face environmental challenges from low oxygen, low temperatures, and high UV radiation. Cashmere fiber and its small size help combat heat loss and energy expenditure. tyrosine hydroxylase (TH, ncbi_102179849) genes may be necessary for regulating the appropriate physiological response to hypoxia in the newborn period(Adams *et al*. 2001). alkaline ceramidase 1 (ACER1, ncbi_102179093) gene, as targeted by key miRNAs, is presumed to enhance energy metabolism due to the function of RNA, allowing for adaptation to hypoxic conditions (Zhang *et al*. 2021). The intensity of light increases with altitude," guanine nucleotide-binding protein beta-1 (GNB1,ncbi_102187070) involved in light transduction pathways are affected by positive selection, possibly in response to greater light intensity (Chi *et al*. 2017).When animals are exposed to hypoxia, they trigger a hypoxia response through a hypoxia-inducible factor (HIF) protein, cyclin-dependent kinase inhibitor Hypoxia-Inducible Factor-1 α (HIF1A, ncbi_100861391)was involved in mediating the physiological responses to oxygen availability (Moraga and Figueroa 2018).

Candidate genes related to disease: The immunoregulatory cytokine interleukin-10 (IL-10, ncbi_100860746) is an important immunosuppressive cytokine, this may represent the evolution of an immune event that reactivates the IL-10 gene under physiological or pathological conditions (Im *et al*. 2004). Selective signals associated with immune responses are considered to be prime targets because they are essential in biological defense against microbial invasion. Some such examples might include interleukin 1A (IL-1A), IL-1B, IL-10, IL-9, IL-4, IL-13, and IL-18 (Schmitt, Klein, and Bopp 2014; Quach *et al*. 2016).Genetic signatures of the human immune response have been widely adapted to regional climates, and these adaptations may lead to disease susceptibility.(Souëf, Goldblatt, and Lynch 2000).In conclusion, it can be concluded that populations using these regulatory variants will have natural selection advantages that affect the consistent activation of immune-related genes.

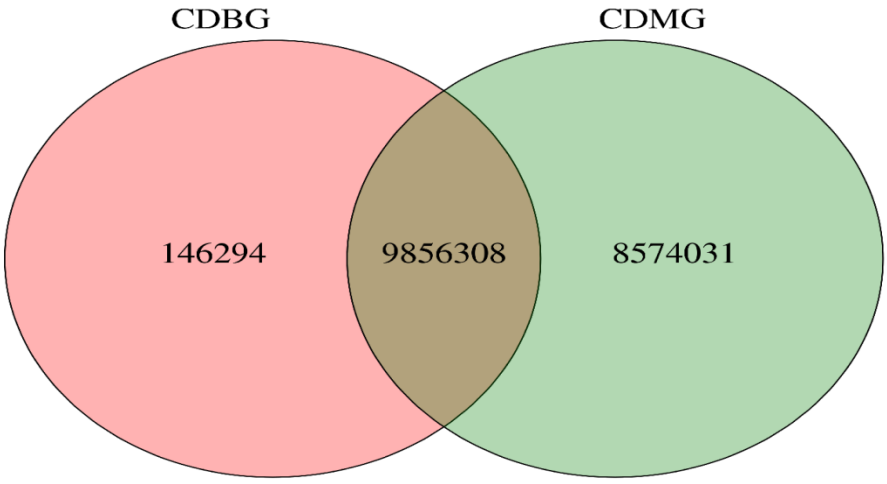

Fig.1 Number of SNPs for the two populations are indicated in the Venn diagram.

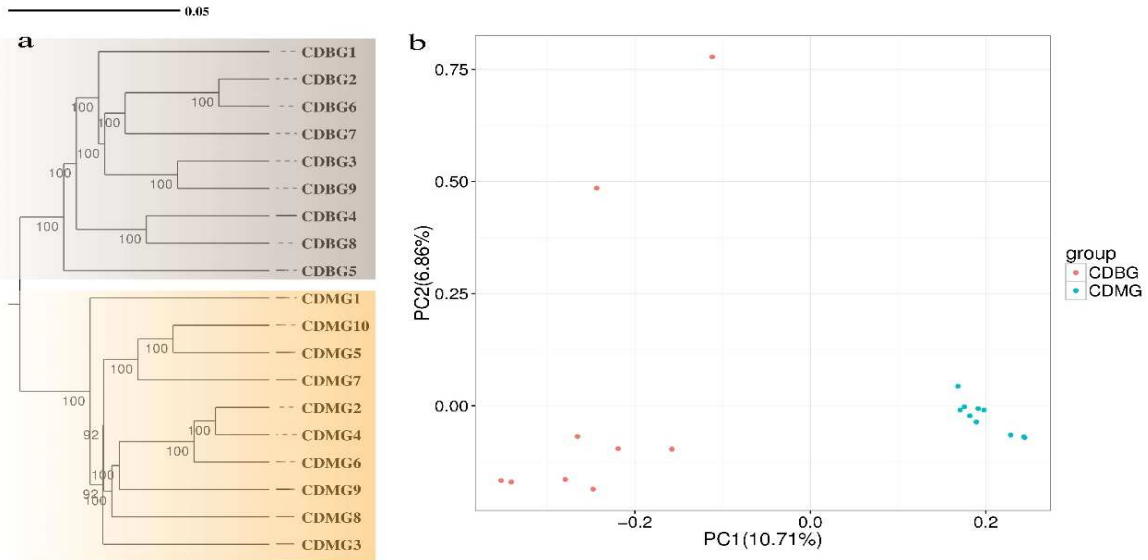

Fig.2 Genome-wide relationship between CDBG and CDMG. (a) Neighbour-joining tree for the 19 goats. The number adjacent to each branch is the bootstrap value. (b) The PCA of the 19 goats. CDBG and CDMG are separated along the first principal component (PC1).

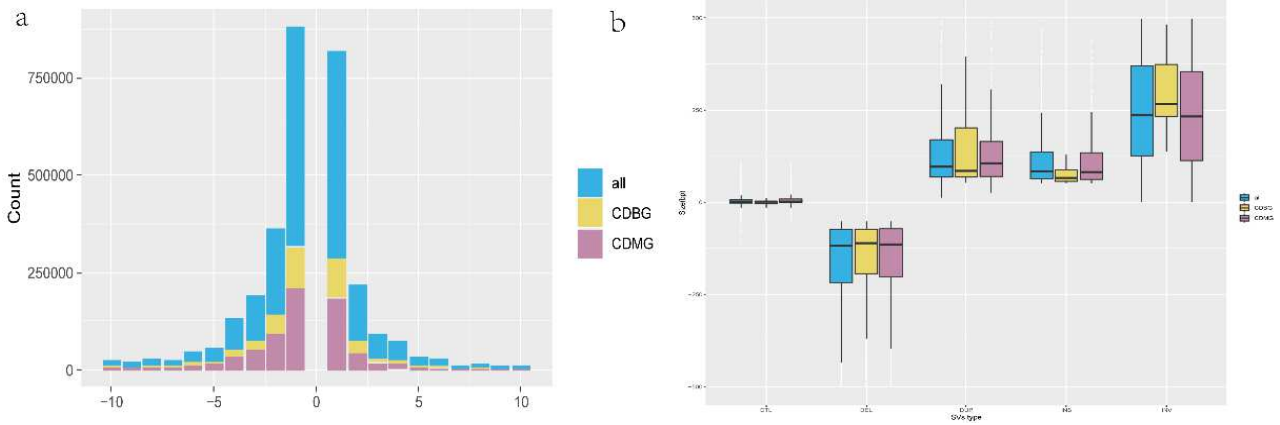

Fig.3 An overview of the variation in goat genome. (a) The relationship between the number of InDels and their size. The CDMG InDels are shown in purple, the CDBG InDels in yellow and the InDels present in both populations in blue.(b) The size distribution of different types of SVs.

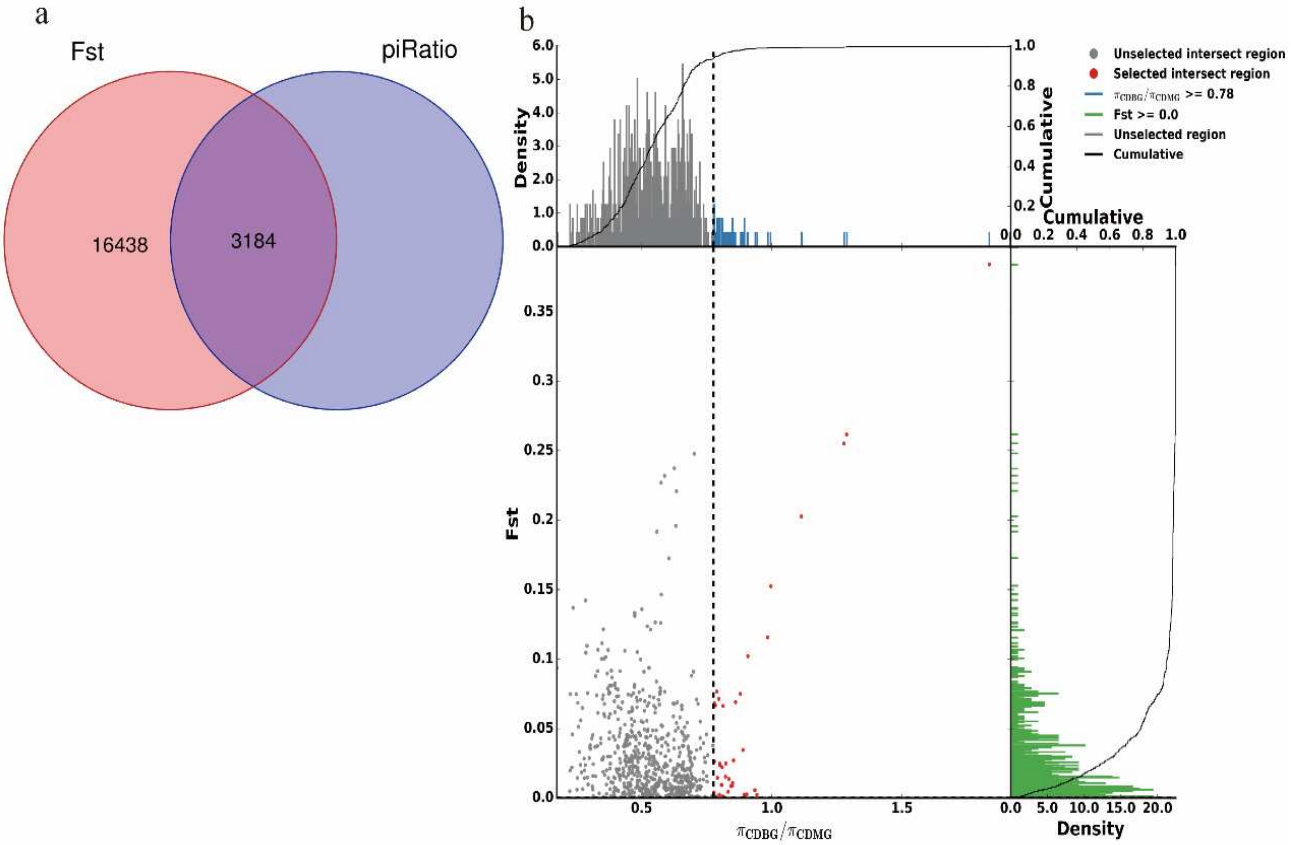

Fig.4 Genomic regions with strong selective signals in CDMG. (a) A Venn diagram detected selected genes via FST or πRation.(b) Distribution of π ratios and FST values calculated in 1000-kbsliding windows with 100-kb increments between CDBG and CDMG. The data points in red (corresponding to the top 5% of the empirical π ratios distribution with values >0.78 and the top 5% of the empirical FST distribution with values >=0) are genomic regions under selection inCDMG.

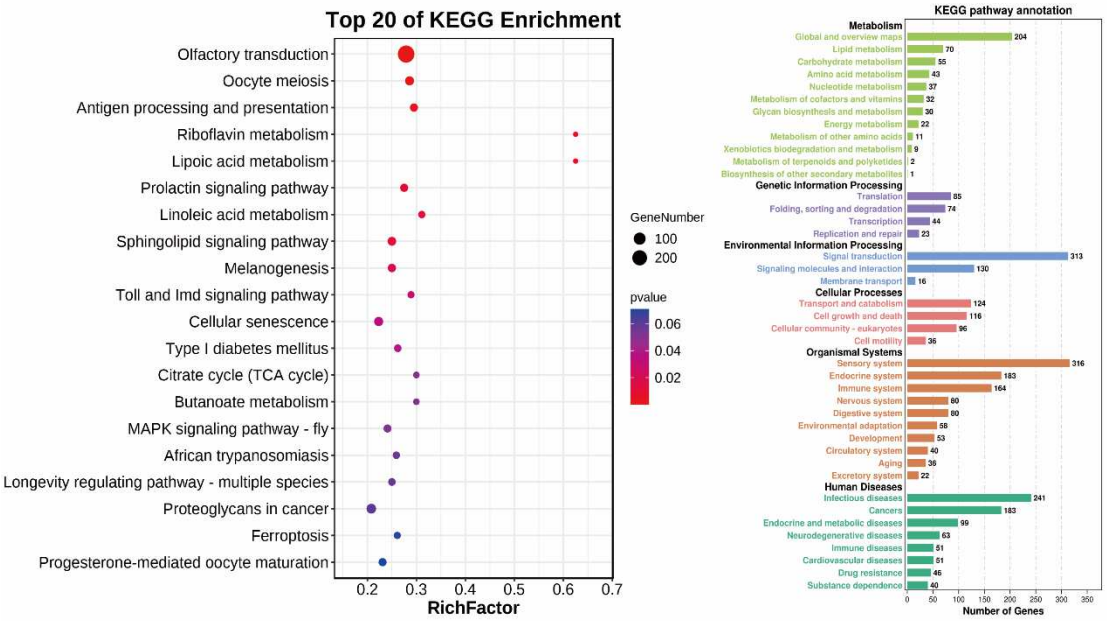

Fig.5 KEGG enrichment analysis of selected genes. (a)Enriched selected genes on twenty KEGG pathways. (b) The number of genes annotated on different KEGG pathways.

Supplementary Table S1

Supplementary Table S1: sequencing reads, alignment statistics and mean genome-wide coverage of each samaple

Sample	Raw Data						Clean Data							
	Raw Reads (M)	Raw Base (Gb)	Raw Q20 (G)	Proportion of Raw Q20 (%)	Raw Q30(G)	Proportion of Raw Q30 (%)	Clean Reads (M)	Proportion of Clean Reads (%)	Clean Base (Gb)	Proportion of Clean Base (%)	Raw Q20 (G)	Proportion of Q20 (%)	Raw Q30(G)	Proportion of Q30 (%)
CDMG1	44742.4089	6711.361	43.6915	97.65%	41.8512	93.54%	44201.9064	98.79%	6630.2860	98.79%	43.2785	97.91%	41.4930	93.87%
CDMG2	43136.8836	6470.533	42.0682	97.52%	40.2428	93.29%	42453.5008	98.42%	6368.0251	98.42%	41.5158	97.79%	39.7535	93.64%
CDMG3	43587.2787	6538.092	42.5750	97.68%	40.8263	93.67%	42755.7834	98.09%	6413.3675	98.09%	41.8780	97.95%	40.2009	94.02%
CDMG4	45690.4266	6853.564	44.6131	97.64%	42.7762	93.62%	45053.8095	98.61%	6758.0714	98.61%	44.1039	97.89%	42.3251	93.94%
CDMG5	42214.2906	6332.144	41.2140	97.63%	39.4912	93.55%	41680.9975	98.74%	6252.1496	98.74%	40.8033	97.89%	39.1340	93.89%
CDMG6	43792.5201	6568.878	42.6978	97.50%	40.8596	93.30%	42769.9680	97.67%	6415.4952	97.67%	41.8396	97.82%	40.0911	93.74%
CDMG7	43209.8235	6481.474	42.2280	97.73%	40.5206	93.78%	42336.3157	97.98%	6350.4474	97.98%	41.4879	98.00%	39.8548	94.14%
CDMG8	44481.2379	6672.186	43.4669	97.72%	41.7620	93.89%	42947.5754	96.55%	6442.1363	96.55%	42.1283	98.09%	40.5474	94.41%
CDMG9	45573.6996	6836.055	44.5278	97.70%	42.7452	93.79%	44594.7256	97.85%	6689.2088	97.85%	43.7034	98.00%	42.0052	94.19%
CDMG10	42034.5357	6305.180	41.0085	97.56%	39.2796	93.45%	41526.5408	98.79%	6228.9811	98.79%	40.6188	97.81%	38.9396	93.77%
CDBG4	20588.1866	3088.228	19.9132	96.72%	18.3006	88.89%	20510.4743	99.62%	3076.5711	99.62%	19.8573	96.82%	18.2600	89.03%
CDBG3	20594.269	3089.140	19.9513	96.88%	18.3712	89.21%	20514.6980	99.61%	3077.2047	99.61%	19.8934	96.97%	18.3291	89.35%
CDBG2	20606.1032	3090.915	19.9410	96.77%	18.3374	88.99%	20522.6061	99.59%	3078.3909	99.59%	19.8804	96.87%	18.2934	89.14%
CDBG9	20460.3186	3069.048	19.7803	96.68%	18.1843	88.88%	20388.0020	99.65%	3058.2003	99.65%	19.7269	96.76%	18.1449	89.00%
CDBG8	20500.1148	3075.017	19.7877	96.52%	18.1423	88.50%	20423.9598	99.63%	3063.5940	99.63%	19.7319	96.61%	18.1016	88.63%
CDBG7	20657.9568	3098.694	19.9284	96.47%	18.2397	88.29%	20585.7010	99.65%	3087.8551	99.65%	19.8759	96.55%	18.2015	88.42%
CDBG6	203810.884	30571.633	19.6690	96.51%	17.9718	88.18%	20297.2784	9.96%	3044.5918	9.96%	19.6086	96.61%	17.9284	88.33%
CDBG5	20548.8718	3082.331	19.7782	96.25%	18.0060	87.63%	20461.4059	99.57%	3069.2109	99.57%	19.7155	96.35%	17.9611	87.78%
CDBG1	20397.064	3059.560	19.7736	96.94%	18.2170	89.31%	20325.0874	99.65%	3048.7631	99.65%	19.7211	97.03%	18.1786	89.44%
Total/ Mean	806626.8740	120994.0311	606.6134	97.16%	574.1251	91.25%	614350.3359	94.13%	92152.5504	94.13%	599.3686	97.35%	567.7431	91.51%

Supplementary Table S2.

Supplementary Table S2.	SNP location information
Type	**Number**
Intergenic	15361008
Intronic	8417688
Exonic	153914
UTR3	141574
Downstream	137810
upstream	134437
UTR5	39334
upstream;downstream	3153
Splicing	576
UTR5;UTR3	66
exonic;splicing	38
synonymous SNV	84818
nonsynonymous SNV	60259
unknown	5914
nonframeshift deletion	690
frameshift deletion	678
stopgain	633
frameshift insertion	503
nonframeshift insertion	366
stoploss	91

Supplementary Table S3. SNP genome location information statistics

Sample	Down stream	Exonic	Exonic, splicing	Intergenic	Intronic	Splicing	Upstream	Upstream; Downstream	UTR3	UTR5	UTR5; UTR3	Non synonymous Snv
CDBG1	39980	45928	2	4412118	2431356	99	37638	889	38807	10029	20	17549
CDBG2	39735	46532	4	4385050	2425074	93	37997	873	38652	10485	19	17621
CDBG3	40634	47491	4	4463198	2452156	100	38965	951	39246	10923	21	18017
CDBG4	40972	46146	3	4480294	2472962	91	38270	914	39189	10299	26	17562
CDBG5	40402	46263	4	4467692	2447420	91	37928	914	39052	10245	26	17542
CDBG6	38994	44639	1	4341777	2385726	88	37036	916	37953	10066	18	16964
CDBG7	39477	44531	3	4416130	2425778	87	36814	900	38643	9746	16	16873
CDBG8	39449	45080	4	4342332	2387806	115	36805	900	38056	9994	22	17191
CDBG9	39995	45449	5	4403162	2424782	96	37086	901	38692	10189	20	17176
CDMG1	45153	53920	2	5191145	2791947	114	43485	1003	43601	12486	22	20378
CDMG10	47155	55746	3	5395309	2902728	116	44838	1121	45232	12821	19	21335
CDMG2	47264	55930	3	5415097	2914979	118	45003	1058	45663	13019	23	21324
CDMG3	46537	55410	2	5402922	2902270	112	44471	1044	45587	12766	23	21111
CDMG4	47577	55779	4	5434632	2926362	111	44938	1072	45964	12823	25	21300
CDMG5	47162	55822	4	5401791	2913759	120	44801	1090	45706	12778	24	21276
CDMG6	46860	55026	5	5395748	2892031	116	43895	1057	45266	12505	26	21055
CDMG7	46511	53900	3	5376376	2879523	109	43552	1002	44264	11944	24	20323
CDMG8	45945	53340	5	5332124	2850983	103	42775	1008	44335	11853	22	20423
CDMG9	46595	55280	8	5372347	2902848	119	44338	1067	45787	12690	10	21019

Supplementary Table S4. Selected regions with high rates of genetic differentiation

Chr	Start	End	Mid	Fst	Pi_ CDBG	Pi_ CDMG	Pi_ CDBG/ Pi_ CDMG	Tajima. D_CDBG	Fu. Li.F_ CDBG	Fu. Li. D_CDBG	theta_ Watterson_ CDBG	Tajima. D_CDMG
1	8900001	9900000	9400000	0	0.002048	0.002558	0.800685	0.778844	1.014825	0.858522	0.001735	0.025865
1	9000001	10000000	9500000	0	0.002276	0.00276	0.824701	0.868949	1.102651	0.933804	0.001898	0.17539
1	9100001	10100000	9600000	0	0.002278	0.002889	0.788649	0.76268	0.985424	0.829355	0.00194	0.287404
1	9200001	10200000	9700000	0	0.002352	0.003027	0.776977	0.754115	0.951316	0.78919	0.002008	0.365054
1	9300001	10300000	9800000	0	0.002517	0.003199	0.786657	0.792896	0.976926	0.805179	0.002134	0.387294
1	9400001	10400000	9900000	0	0.002599	0.003288	0.790557	0.805108	0.999418	0.828743	0.002199	0.377579
1	9500001	10500000	10000000	0	0.002665	0.003375	0.789612	0.681974	0.91194	0.76984	0.002276	0.385108
1	9600001	10600000	10100000	0	0.002738	0.00346	0.791214	0.671441	0.917426	0.781305	0.002344	0.392482
1	9700001	10700000	10200000	0	0.002806	0.003474	0.807638	0.673503	0.914827	0.776966	0.002403	0.418192
1	9800001	10800000	10300000	0	0.002804	0.003485	0.804575	0.716612	0.926584	0.774175	0.002382	0.433993
1	9900001	10900000	10400000	0	0.002905	0.003679	0.789716	0.687593	0.872289	0.716677	0.002483	0.390925
1	10100001	11100000	10600000	0	0.002641	0.003377	0.782171	0.67079	0.855673	0.701403	0.002264	0.08558
1	10200001	11200000	10700000	0	0.002635	0.003381	0.779395	0.662505	0.874539	0.729323	0.002261	-0.02889
1	10300001	11300000	10800000	0	0.00272	0.003474	0.782871	0.63462	0.864916	0.728944	0.002349	-0.04354
1	10400001	11400000	10900000	0	0.002809	0.00359	0.782462	0.615557	0.834581	0.698176	0.002435	-0.03259
1	10700001	11700000	11200000	0	0.003047	0.003917	0.777713	0.662653	0.90146	0.763817	0.002617	0.091319
1	10900001	11900000	11400000	0	0.00312	0.003943	0.791313	0.641696	0.930041	0.81028	0.002696	0.161561
1	11000001	12000000	11500000	0	0.003236	0.004007	0.807483	0.71062	0.991116	0.859083	0.002761	0.233073
1	11100001	12100000	11600000	0	0.003242	0.004045	0.801439	0.681013	0.963513	0.836191	0.002784	0.268433
1	11200001	12200000	11700000	0	0.003171	0.003926	0.807859	0.668833	0.933448	0.800162	0.002738	0.277162
1	11300001	12300000	11800000	0	0.00302	0.003814	0.79182	0.700496	0.951171	0.809293	0.002591	0.274538
1	11400001	12400000	11900000	0	0.003093	0.003932	0.786571	0.722999	0.951028	0.799329	0.002643	0.250772

Supplementary Table S5. Gene Ontology enrichment analysis of the 1867 candidate genes embedded in the selected regions

Category	p_value	q_value	NumDEInCa	NumInCat	Term	Class	Gene_id
GO:00076(	0.000000	0.000000	234	681	sensory per	Biological	ncbi_102168442(LOC102168442);ncbi_102168494(UBR3);ncbi_102
GO:00509(	0.000000	0.000000	217	634	detection o	Biological	ncbi_100860822(CRSP-2);ncbi_100861135(LXN);ncbi_100861290((
GO:00509(	0.000000	0.000000	212	619	detection o	Biological	ncbi_102168442(LOC102168442);ncbi_102168540(LOC102168540)
GO:000959	0.000000	0.000000	214	635	detection o	Biological	ncbi_102168442(LOC102168442);ncbi_102168540(LOC102168540)
GO:00516(	0.000000	0.000000	219	663	detection o	Biological	ncbi_100860822(CRSP-2);ncbi_100861135(LXN);ncbi_100861290((
GO:00076(	0.000000	0.000000	273	915	sensory per	Biological	ncbi_100860822(CRSP-2);ncbi_100861024(CRYM);ncbi_10086113
GO:00508	0.000000	0.000000	297	1077	neurologica	Biological	ncbi_100860822(CRSP-2);ncbi_100861024(CRYM);ncbi_10086113
GO:00030(	0.000000	0.000000	347	1411	system pro	Biological	ncbi_100860822(CRSP-2);ncbi_100860827(AR);ncbi_100861024(CF
GO:00071(	0.000000	0.000000	415	2010	cell surface	Biological	ncbi_100860827(AR);ncbi_100860996(MAPK13);ncbi_100861232(T
GO:00422	0.000000	0.000021	445	2246	response to	Biological	ncbi_100860759(AMELX);ncbi_100860794(LEP);ncbi_100860813(I
GO:00071(	0.000001	0.000460	634	3419	signal trans	Biological	ncbi_100860794(LEP);ncbi_100860807(KITLG);ncbi_100860822(Cl
GO:00325(	0.000002	0.000687	749	4123	multicellul	Biological	ncbi_100860748(LOC100860748);ncbi_100860759(AMELX);ncbi_1
GO:00230	0.000015	0.004101	651	3578	signaling	Biological	ncbi_100860794(LEP);ncbi_100860807(KITLG);ncbi_100860822(Cl
GO:00447(	0.000016	0.004119	650	3574	single orga	Biological	ncbi_100860794(LEP);ncbi_100860807(KITLG);ncbi_100860822(Cl
GO:00071	0.000037	0.008773	655	3626	cell commu	Biological	ncbi_100860794(LEP);ncbi_100860807(KITLG);ncbi_100860822(Cl
GO:00508	0.000053	0.011935	874	4973	response to	Biological	ncbi_100860759(AMELX);ncbi_100860794(LEP);ncbi_100860807(I
GO:00517	0.000152	0.032104	681	3824	cellular res	Biological	ncbi_100860794(LEP);ncbi_100860807(KITLG);ncbi_100860822(Cl
GO:00108(	0.000482	0.091049	9	17	positive reg	Biological	ncbi_102169016(PRKCE);ncbi_102170997(SELE);ncbi_102174105(
GO:19002	0.000482	0.091049	9	17	regulation (	Biological	ncbi_102169016(PRKCE);ncbi_102170997(SELE);ncbi_102174105(
GO:00002(	0.000544	0.092916	5	6	mitochondr	Biological	ncbi_100861340(FIS1);ncbi_102175019(CCAR2);ncbi_102180018(D
GO:00327	0.000544	0.092916	5	6	DNA meth	Biological	ncbi_100861294(DNMT1);ncbi_102178316(EHMT2);ncbi_1021862
GO:00105	0.000570	0.092916	14	35	regulation (	Biological	ncbi_102168396(ARF4);ncbi_102169016(PRKCE);ncbi_102170997(

Supplementary Table S6. Top 21 enriched pathway

KEGG_A_	KEGG_B_	Pathway	CDBG_vs_	All (8322)	Pvalue	Qvalue	Pathway ID	Genes	K_IDs
Organisma	Sensory sy	Olfactory t	289	1037	1.79E-22	5.86E-20	ko04740	ncbi_1021	K04257+K04257+K04257+K04257+K04257-
Cellular Pr	Cell growth	Oocyte mei	34	119	0.000773	1.26E-01	ko04114	ncbi_1008	K08557+K04441+K08043+K08046+K02602-
Human Dis	Immune di	Graft-versu	19	58	0.001991	2.17E-01	ko05332	ncbi_1008	K06752+K04519+K03156+K04383+K06751-
Organisma	Immune sy	Antigen pr	23	78	0.003362	2.21E-01	ko04612	ncbi_1008	K06752+K03283+K08056+K03156+K06751-
Metabolisn	Metabolisn	Riboflavin	5	8	0.004618	2.21E-01	ko00740	ncbi_1008	K14394+K00861+K01513+K01513+K14379
Metabolisn	Metabolisn	Lipoic acid	5	8	0.004618	2.21E-01	ko00785	ncbi_1021	K01896+K01896+K01896+K01896+K01896
Human Dis	Immune di	Asthma	10	25	0.00473	2.21E-01	ko05310	ncbi_1008	K05443+K06752+K05430+K03156+K05432-
Organisma	Endocrine	Prolactin si	22	80	0.009966	4.07E-01	ko04917	ncbi_1008	K05439+K04441+K05439+K04503+K04364-
Metabolisn	Lipid metal	Linoleic ac	14	45	0.012226	4.11E-01	ko00591	ncbi_1021	K07424+K14621+K16817+K16817+K07424-
Environme	Signal tran	Sphingolip	30	120	0.012559	4.11E-01	ko04071	ncbi_1008	K04441+K03156+K04718+K18050+K03456-
Human Dis	Infectious	Malaria	15	52	0.019794	5.01E-01	ko05144	ncbi_1008	K05443+K06508+K04519+K05482+K03156-
Organisma	Endocrine	Melanogen	25	100	0.021391	5.01E-01	ko04916	ncbi_1008	K05461+K04492+K08043+K01357+K08046-
Human Dis	Endocrine	Cushing sy	36	156	0.023378	5.01E-01	ko04934	ncbi_1008	K04492+K04684+K09187+K08043+K01357-
Human Dis	Drug resist	Endocrine	24	96	0.023824	5.01E-01	ko01522	ncbi_1008	K04684+K04441+K08043+K08046+K04503-
Human Dis	Infectious	Leishmania	18	68	0.027176	5.01E-01	ko05140	ncbi_1008	K05443+K06752+K05430+K04519+K03990-
Human Dis	Infectious	Epstein-Ba	47	215	0.02752	5.01E-01	ko05169	ncbi_1008	K05443+K06752+K03283+K04441+K03008-
Human Dis	Infectious	Pertussis	19	73	0.028007	5.01E-01	ko05133	ncbi_1008	K05443+K04519+K03990+K04441+K03156-
Organisma	Immune sy	Toll and In	13	45	0.02859	5.01E-01	ko04624	ncbi_1008	K04441+K10380+K20703+K04733+K06689-
Human Dis	Drug resist	Antifolate	16	59	0.029087	5.01E-01	ko01523	ncbi_1008	K04519+K03156+K13649+K13649+K13649-
Cellular Pr	Cell growth	Cellular se	37	166	0.035727	5.84E-01	ko04218	ncbi_1008	K04441+K04383+K07208+K03982+K15040-

Conclusion: To our knowledge, Genome-wide scanning revealed the genomic footprint of candidate genes involved in phenotypic traits and hypoxic adaptation. The candidate genes identified in the selected region were associated with the phenotypes incashmere fiber traits, reproduction traits, body size, high-altitude adaptation, and disease, indicating the genetic basis of phenotypic evolution adapted to local climatic conditions. Furthermore**, t**hese results lay a foundation for further study on genetic diversity and genomic characterization of essential traits of Qaidam cashmere goats.

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Authors' contributions: DQ and KZ arrange experiments and implement projects. DT analyzed the data and wrote the paper. BZ and FT participated in the data analysis. BHand XL did preliminary work of the experiment and data collation and analysis. All authors reviewed and agreed to the final manuscript.

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Availability of data and materials: The original data measured in this study were stored in NCBI SRA with the accession number SRASUB9339333 under Bio-project PRJNA723729.

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