Whole-Genome Selective Scans Detect Genes Associated With Important Phenotypic Traits in Sheep (Ovis aries)

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Sheep (Ovis aries) is one of the important livestock with diverse phenotypic traits. However, little is known about the molecular mechanism of diverse phenotypic traits in domestic sheep. Using the genome-wide high-density SNP data (600K) in 253 samples from 13 populations, we conducted the tests of selective sweeps (i.e., pairwise $F_{ST}$ and XP-CLR) associated with several important phenotypic traits (e.g., tail types, horn morphology, prolificacy, coat pigmentation, ear size, milk production, meat production, body size and wool fineness). We identified strong selective signatures in previously reported (e.g., $T$, RXFP2, BMPR1B, TYRP1, MSRB3, TF, CEBPA, GPR21 and HOXC8) and novel genes associated with the traits, such as CERS6, BTG1, RYR3, SLC6A4, NNAT and OGT for fat deposition in the tails, FOXO4 for fertility, PTCH1 and ENMX2 for ear size, and RMI1 and SCD5 for body size. Further gene annotation analysis showed that these genes were identified to be the most probable genes accounting for the diverse phenotypic traits. Our results provide novel insights into the genetic mechanisms underlying the traits and also new genetic markers for genetic improvement in sheep and other livestock.

Keywords: artificial selection, genome-wide SNPs, sheep, phenotypic traits, genetic improvement

INTRODUCTION

Sheep (Ovis aries) is an excellent model species for investigating the genetic basis of diverse phenotypic traits under the effects of genetic drift, natural and artificial selection factors (Cao et al., 2020). Following domestication, as many as 1,400 breeds have been developed in sheep (Scherf, 2000). In particular, human-imposed selection has affected the species greatly over the past hundreds of years, and, thus, diverse phenotypic traits have been formed in different breeds, such as fat-rumped sheep (Kazakh Edilbai), thin-tailed sheep (Celle Black), Polled (Merino), high prolificacy sheep (Hu) and dairy sheep (Lacaune) (Wei et al., 2015; see Table 1).

The recent availability of genome-wide SNPs gave a new momentum to identify the genetic variants underlying phenotypic traits (Kijas et al., 2012; Xu and Li 2017; Gui et al., 2020; Abousoliman et al., 2021; Zhou et al., 2021). Previous studies have identified a number of candidate genes or variants associated with meat, growth, milk, wool, reproduction, horns and tails in sheep, most of which have employed the low-density SNPs (50K) (see the review in Xu and Li, 2017) or whole-genome sequences (Li et al., 2020). However, to date, little is known regarding the
TABLE 1 | Summary information of 13 breeds of domestic sheep.

| Breed origin | Breed name       | Code | No. of samples | Sex    | Phenotypic characteristics                                      | Geographic origins |
|--------------|------------------|------|----------------|--------|----------------------------------------------------------------|--------------------|
| China        | Celle Black Sheep| CLS  | 15             | Female | Short thin-tailed and black or gray coat color                   | 34.02  82.66       |
| China        | Tan sheep        | TAN  | 15             | Female | White coat color and seasonal reproductive                      | 37.75  106.41      |
| China        | Hu sheep         | HUS  | 15             | Female | High prolificacy                                                  | 32.44  120.25      |
| Kazakhstan   | Kazakh Edilbai    | KAZ  | 9              | Female | Fat-rumped and a wide and deep body                              | 52.32  77.03       |
| Afghanistan  | Jill Wagner sheep | WGJ  | 11             | Male/Female | Exceptionally large and floppy ears                       | 37.13  79.93       |
| Scotland     | Shetland         | SHL  | 11             | Male/Female | Medium length legs and finely boned                        | 51.17  4.20        |
| Australia    | Merino           | MER  | 36             | Male   | Two horns                                                       | −25.27 123.78      |
| Australia    | Polled Merino    | PME  | 19             | Male   | Homeliness                                                      | −25.27 133.78      |
| France       | Meat Lacaune     | LAM  | 34             | Female | Meat type                                                       | 43.97  2.99        |
| France       | Dairy Lacaune    | LAC  | 36             | Female | Dairy type                                                      | 43.97  2.99        |
| Germany      | East Friesian sheep | EFR | 22             | Female | Dairy type                                                      | 49.82  15.47       |
| Russia       | Caucasian        | CAU  | 15             | Female | Delicate wool                                                    | 45.71  42.88       |
| Italy        | Altamurana       | ALT  | 15             | Female | Semi-fine wool                                                  | 41.12  16.87       |

FIGURE 1 | Images of domestic sheep (A) Kazakh Edilbai sheep (B) Celle Black sheep (C) Polled Merino (D) Merino (E) Hu sheep (F) Tan sheep (G) Caucasian sheep (H) Altamurana sheep (I) Jill Wagner sheep (J) Meat Lacaune (K) Dairy Lacaune (L) Shetland (M) East Friesian sheep. Photo credits are showed in supplementary table 2.
molecular mechanism of diverse phenotypic traits in sheep, such as dairy and horn traits within breeds. Here, we applied genome-wide selective scans to detect critical genes associated with the phenotypic traits based on the Ovine Infinium HD BeadChip.

**Materials and Methods**

**Genotypic and Phenotypic Data**

We collected 253 individuals from 13 domestic sheep populations with typical phenotypic traits to investigate the genetic variants under long-term artificial selection (Figure 1 and Table 1; Kijas et al., 2014; Xu et al., 2017; Zhao et al., 2017; Gao et al., 2018; Xu et al., 2018; Rochus et al., 2018; Cao et al., 2020). Whole genome SNP datasets (Ovine Infinium HD SNP BeadChip) of these individuals were obtained from previous studies (Xu et al., 2017; Zhao et al., 2017; Gao et al., 2018; Xu et al., 2018) and divided into 9 pairs of populations (Table 2). We performed two different selection methods, the pairwise FST (Weir and Cockerham, 1984) and the cross-population composite likelihood ratio (XP-CLR) test (Chen et al., 2010). The identification of common signatures by the different algorithms and assumptions might be seen as good reliability of the results while reducing the likelihood of false positives.

**SNP Data Quality Control**

We implemented strict quality control of the SNP dataset using the PLINK v1.09 software (Purcell et al., 2007). We removed individuals and SNPs that met any of the following criteria: 1) SNPs without chromosomal or physical locations; 2) SNPs with >0.02 missing data; 3) individuals with a genotyping rate <0.95; 4) minor allele frequency (MAF) < 0.05; and 5) the p-value of Fisher’s exact test for Hardy-Weinberg equilibrium (HWE) < 0.00001. Consequently, the final data after filtering contained various sets of SNPs and individuals in the comparison tests, such as 506,350 SNPs and 24 individuals (9 Kazakh Edilbai sheep vs 15 Celle Black Sheep) for the trait of tail shape, 485,747 SNPs and 55 individuals (36 Merino sheep vs 19 Polled Merino sheep) for horn morphology, 514,795 SNPs and 30 individuals (15 Hu sheep vs 15 Tan sheep) for fertility, 509,580 SNPs and 30 individuals (15 Celle Black sheep vs 15 Tan sheep) for wool fineness, 519,650 SNPs and 20 individuals (11 Jill Wagner sheep vs 9 Kazakh Edilbai sheep) for ear size, 483,150 SNPs and 70 individuals (34 Meat Lacaune sheep vs 36 Dairy Lacaune sheep) for meat production, 528,576 SNPs and 20 individuals (9 Kazakh Edilbai sheep vs 11 Shetland sheep) for body size, 471,257 SNPs and 31 individuals (16 East Friesian sheep vs 15 Caucasian sheep) for milk production (Supplementary Table S1).

**Genomic Selection Signals Analysis**

To identify the genomic signatures of selection between pairwise populations of contrasting these phenotypes in domestic sheep, we calculated the FST values (Weir and Cockerham, 1984) for each SNP using the program Genepop v4.2 (Rousset, 2008). We took the top 0.02% of the empirical distribution of FST as the putative selective signals. Further, we calculated the XP-CLR scores for the 200 bp intervals along the chromosomes using the parameters (“-w 0.005200” 2000-p 0 0.95”). For each chromosome, we averaged the XP-CLR scores per window across non-overlapping 10 kb windows. We selected the top 0.05% of these windows as the putative selective regions.

**Results and Discussion**

We implemented selection screening in 9 pairs of populations: KAZ and CLS for tail types, PME and MER for presence or absence of horn, HUS and TAN for fertility, CLS and TAN for coat colors, ALT and CAU for wool fineness, WGF and KAZ for ear size, LAC and LAM for meat types, KAZ and SHL for body size and EFR and CAU for milk production. We detected significant common signals located within or neighboring both novel and previously reported functional genes. A total of 36 genes were shared between the two selection scan metrics (Table 2). For example, seven genes (CERS6, BTG1, RYR3, T, SLC6A4, NNAT, OGT) (Figure 2 and Supplementary Tables 3, 4) were identified to be associated with different tail shapes (i.e., fat-tailed vs thin-tailed) (Joo and Yun, 2011; Tsai et al., 2013; Ruan et al., 2014; Xiao et al., 2016; Dias et al., 2016; Turner et al., 2018; Zhi et al., 2018). In the horned vs polled sheep, the well-known horn morphology-associated gene RXFP2 has been implicated as a strong candidate gene that explains the presence or absence of horn in sheep (Figure 3 and Supplementary Tables S5, S6; Hu et al., 2019). In the high prolificacy vs low prolificacy breeds, the gene BMPR1B could be involved in the variation in litter size of females.
In addition, the two genes TYRP1 and KIT had been directly implicated in the mechanism of coat-colour pigmentation in the white vs non-white coat-colour breeds (Supplementary Figure S2 and Supplementary Tables S9, 10; Vage et al., 2003). The five genes MSII, DSG1, HOXC8, HOXC12 and HOXC13 were crucial regulators for wool fineness in the fine-wool vs semi-fine wool sheep (Supplementary Figure S3 and Supplementary Tables S11, 12; Awgulewitsch, 2003). The genes MSRB3, PTCH1 and EMX2 were functionally associated with ear size in the large and floppy vs normal ears sheep (Supplementary Figure S4 and Supplementary Tables S13, 14; Rhodes et al., 2003; Wei et al., 2015; Shin et al., 2017). The eleven genes (CEBPA, CEBPG, DLX3, DLX4, GBAS, NSMAF, PDE3A, PEPD, SDCBP, TNRC6A and UTRN) had been reported to be involved in regulating meat production such as intramuscular fat, drip loss, marbling score, meat traceability and longissimus muscle in the meat-type vs non-meat-type sheep (Supplementary Figure S5 and Supplementary Tables S15, 16; Lobbert et al., 1996; Nonneman et al., 2013; Ayuso et al., 2015). The genes RMI1, GPR21, SCD5 and CADM1 might play important roles in regulating embryo development, body weight, lipid metabolism and energy homeostasis involved in differences in body size (Supplementary Figure S6 and Supplementary Tables S17, 18; Guo et al., 2013). The gene TF was associated with milk production in the dairy-type vs non-dairy-type sheep (Supplementary Figure S7 and Supplementary Tables S19, 20; Ju et al., 2011).

In particular, we detected novel genes with functions associated with specific traits in sheep, such as CERS6, BTG1, NNAT and OGT for fat deposition in the tail of sheep, FOXO4 for fertility, PTCH1 and EMX2 for ear size, and SCD5 for body size. As a negative regulator of β-oxidation, the expression of CERS6 was significantly increased in subcutaneous fat of obese subjects with type 2 diabetes (Raichur et al., 2019). The BTG1 gene plays a key role in intramuscular fat deposition by regulating adipose-derived stem cell differentiation to
osteocytes and myocytes (Moisa et al., 2015). The gene **NNAT**, as an endoplasmic reticulum proteolipid implicated in the intracellular signalling, is associated with severe obesity (Scott et al., 2013). The gene **OGT** is an important determinant of fatty acid synthesis in the mouse liver, which plays a critical role in fat deposition (Guinez et al., 2011; Kos et al., 2009). The **FOXO4** gene has an important role in the activity of corpus luteum that is linked to folliculogenesis (Pisarska et al., 2009). The **PTCH1** gene plays a critical role in the microcephaly, developmental delay, short stature, and facial dysmorphism by stimulating sonic hedgehog homolog (SHH) pathway (Derwinska et al., 2009). The **EMX2** gene is highly expressed in mouse inner ear, with the role of activating early hair cell development (Holley et al., 2010). The **SCD5** gene is linked to the regulator of sterol regulatory element-binding proteins involved in the development of body size (Baeza et al., 2013). Taken together, the apparent differences in the phenotypic traits among the breeds might be explained by diverse regulation mechanisms.

Noteworthy, we did not detect previously reported important functional genes associated with specific traits, for example, **PDGFD** and **BMP15**, which are associated with fat deposition in the tails of sheep (Li et al., 2020) and litter size (Xu et al., 2018), respectively. The main reason could be complex genetic mechanisms of phenotypic traits, for example, fertility was regulated by different major functional genes **BMP15**, **NCOA1** and **NF1** for Wadi, Icelandic and Finnsheep, respectively (Xu et al., 2018). In addition, we identified candidate functional genes different from those identified in earlier investigations, which could be due to that the power for general linear models to detect such associations will be weak when treating quantitative traits given the small sample size (Xu et al., 2018). Furthermore, these breeds could have been subjected to selection on specific traits (e.g., body weight)
through environmental variables such as climate, diet and diseases. However, we did not obtain detailed information for these variables in our data analysis. Thus, these variables were not taken into account in our data analysis, which would be essential for future study.

In conclusion, we detected some novel and previously reported functional genes associated with particular essential for future study. Nevertheless, associations between these genes detected in two tests and the specific traits should be worthy of further exploration in future investigations. These findings contribute to understanding of the genomic consequences of artificial selection in the genomes of domestic sheep.

DATA AVAILABILITY STATEMENT

The original contributions presented in the study are included in the article/Supplementary Material further inquiries can be directed to the corresponding author.

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AUTHOR CONTRIBUTIONS

FL and S-SX conceived and designed the project. LG and MS collected the samples. S-SX and LG analyzed the data. S-SX and LG wrote the manuscript with contributions from FL.

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SUPPLEMENTARY MATERIAL

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