A genome-wide scan to detect signatures of recent selection in Australian Merino sheep

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Abstract   Domestication and selection are processes that conserve the pattern of genetic diversities between and within populations. Identification of genomic regions that are targets of selection for phenotypic traits is one of the main aims of research in animal genetics. An approach for identifying divergently selected regions of the genome is to compare F_{ST} values among loci to estimate the genetic variability between and within populations. In this study, a whole genome scan using the 50K Illumina Ovine SNP chip was performed in seventeen flocks of Australian Merino sheep (8 CRC flocks and 9 SG flocks). Population differentiation using F_{ST} in these flocks revealed seven genomic regions. These areas were located on chromosomes 2 (two region), 3, 6, 7, 16 and 26 (Wintheta> 0.15). In this study, a number of candidate genes associated with reproductive and growth traits were identified. Study of the reported QTLs in these regions of the ovine and bovine genomes also showed that they associated with important traits such as reproduction, carcass yield, growth and wool traits. Further validation studies of these regions can be used to identify the candidate genes for economically important traits in sheep breeds. The results also provided intuitions for further understanding of the genetic diversities among the Merino flocks.

Keywords: Australian Merino sheep, genomic scan, population differentiation, signatures of selection

Introduction

Small ruminants, especially native breed types, play an important role in the livelihood of a considerable section of human population in the tropics from socio-economic aspects. Therefore, integrated attempt in terms of management and genetic improvement to enhance production is of crucial importance (Mohammadabadi and Sattayimokhtari, 2013). Economical and biological efficiency of sheep production enterprises is generally improved by increasing ewe productivity and reproductive performance (Soufy et al., 2009; Vajed Ebrahimi et al., 2017). Efficiency of selection for growth performance could be improved by the use of molecular genetics methods, because genomic data provide valuable information for genetic evaluation of animals (Zamani et al., 2015).

Sheep is the first livestock species domesticated nearly 9000 years ago (Chessa et al., 2006). The wide distribution of this species is a concept of their adaptability to different environments and this has resulted in enormous morphological variation among populations (Diamond, 2002; Kijas et al., 2009). After domestication, natural and artificial selection processes led to a

wide range of phenotypes and resulting different animal strains (Kijas et al., 2009). Selection for increasing of frequency in new mutations that are advantageous only in a subset of populations leaves some signatures in the genome (Hancock et al., 2008). Detecting these genomic regions is of great importance in animal genetics, particularly in species where few annotated genes are available (Lee et al., 2013). Understanding the genes are under selection and their pathways can be achieved by discovering these features. In addition, the locations of selection signatures are often correlated with QTL affecting economically important traits (Moradi et al., 2012). The need to maintain and improve local genetic resources has been recognized as a priority, at the world level. Biodiversity studies depicting a deep picture of the genetic variability of the available sheep breeds provide favorable opportunities for both genetic conservation programs as well as enhancing production efficiency by means of controlled and well-designed cross-breeding systems exploiting breed diversities, heterosis and breed complementarity (Mohammadabadi et al., 2010a; Vajed Ebrahimi et al., 2017). Maintenance of genetic diversity in livestock species requires adequate implementation of conservation priorities and sustainable management programs, which should be based on comprehensive information regarding the structure of the populations, including sources of genetic variability among and within breeds (Mohammadabadi et al., 2010b).

The study of genes underlying phenotypic variation can be performed in two different directions. Firstly, from phenotype to genome, which is performed by linkage disequilibrium (LD) based association QTL mapping or candidate genes identification. Secondly, from genome to phenotype, performed by statistical evaluation of genomic data to identify regions under selection (Akey et al., 2009; Qanbari et al., 2010). The second approach identifies patterns of LD in or between populations, which are incompatible with the hypothesis of the genetic neutrality, and are known as selective sweeps or selection signatures. Recently a number of studies have been performed to detect signals of recent positive selection on a genome-wide scan in pig (Amaral et al., 2011; Rubin et al., 2012), cattle (Hayes et al., 2009; Qanbari et al., 2011; Sorbolini et al., 2015) and sheep (Moradi et al., 2012; Kathryn et al., 2014). Moradi et al. (2012) performed a genome scan from 90 sheep to search for signatures of divergent selection using F_{ST} in Iranian fat and thin-tailed sheep breeds. Most of the regions identified were associated with QTL reported for carcass traits. Two analytical methods including F_{ST} (Fisher, 1925) and Peddrift (Dodds and McEwan, 1997)

have been used to detect differentiation between selected lines of Romney and Perendale sheep (Kathryn et al., 2014). In this study, fourteen novel regions which are associated with resistance or susceptibility to gastrointestinal nematodes were identified. In addition, Qanbari et al. (2010) reported regions associated with candidate genes and QTL such as milk yield, reproductive and behavioral traits in Holstein cattle.

If the mutation is recent and the selection is strong, alleles on the homogeneous chromosome segment as the mutant allele will be increased. However, a novel mutation under selection increases rapidly in allele frequency, so that the conserved haplotype is long (Nielsen, 2005). The quick increase in frequency to fixation of a useful allele can reduce its signature at neutral connected loci (Kim, 2006). This means that, the genomic regions that display high F_{ST} values compared with the neutral loci have been under selection (Porto-Neto et al., 2013). The F_{ST} values related to the distinctive regions are expected to come from different distributions; higher F_{ST} values reflecting different selection and lower F_{ST} values reflecting balancing selection, respectively. This can be estimated by clustering a set of F_{ST} values from a multi population analysis. Selected loci can be detected based on LD such as Extended Haplotype Homozygosity (EHH) and Relative EHH (REHH) or population differentiation (such as F_{ST} and theta) methods (Wright, 1992; Sabeti et al., 2002). The methods based on LD start with identification of the core haplotypes (through genotyping a set of SNPs in a region so small that recombination may not occur).

Common signatures of selection can be detected in different animal populations using F_{ST} analysis. Identification of candidate genes and QTL in the regions under selection can be used to further understand the genetic basis of economically important traits. The animal genomes can be scanned for recent positive selections using the available large scale SNPs data. The aim of this study was to detect selective sweeps in the Australian Merino sheep using the dense Illumina OvineSNP50 Bead chip, and their concurrence with the reported QTL and candidate genes in the ovine genome.

Material and methods

Sample collection and genotyping

Blood samples were collected from 3974 Australian Merino sheep. The animals were from seventeen flocks including 8 CRC flocks and 9 SG flocks. The Illumina 50K Ovine SNP chip (Illumina Inc., San Diego, USA) containing 48599 single nucleotide polymorphisms (SNPs) were used to genotype the animals. Samples for

genotyping were collected under approval number AEC12-049 of the University of New England Animal Ethics Committee.

Data quality control

To ensure the overall quality of the samples and a consistent set of genotypes, filtering was applied to the primary data using Plink v1.07 software (Purcell et al., 2007). After applying the quality control measures, 48468 SNPs were retained. The SNPs with the call rate less than 0.95, the Illumina Gentrain score less than 0.95, the minor allele frequency (MAF) less than 0.01 and not in Hardy-Weinberg equilibrium (a P-value cutoff of 1×10^{-6}) were removed. The Bonferroni correction ($\beta = \alpha/n$) was used to address the problem of multiple comparisons (Abdi, 2007). A conservative significance level ($\alpha = 0.05$) was applied, and the number of tests was equal to be the number of SNPs (n = 48,599). Then a value of 10^{-6} was calculated for β.

Statistical analyses and selection signatures detection

The principal component analysis (PCA) was used to reduce the dimensionality of large data sets. The PCA was performed using the PRCOMP function in R software (R Core Team, 2011). The PCA in Australian Merino sheep data set was calculated on GRM. To evaluate genetic differentiation for each locus, the loci with positive selection were detected based on fixation index (F_{ST}). The F_{ST} values were computed using R software. The F_{ST} is a measure of population differentiation which was calculated as described by MacEachern et al. (2009):

$$F_{ST} = H_T - H_S/H_T$$

where, H_T denotes the expected heterozygosities for total populations and H_S denotes the expected heterozygosities in subpopulations.

One of the main problems with the Wright's F_{ST} estimator (Wright, 1951) is that it does not account for the sampling error. This was corrected for by Weir and Cockerham (1984) who developed the unbiased estimator (θ); the method that was used in this research. Signatures of selection were identified using significant threshold of 0.15 for the theta -window values. As individual SNP may not show a strong signal, a 5-SNP moving average (WIN5) was used to identify regions with strong signatures of selection over multiple SNPs, which also reduces noise (Weir et al., 2005). An arbitrary window of 5 markers (~300 Kbp) was selected as it appeared to provide a better signal. To compute the

genetic divergence among all populations, pairwise F_{ST} was also calculated with the unbiased estimator (Weir and Cockerham, 1984). The ape package was used to create Neighbor joining (NJ) graph (R Core Team, 2014).

Study of genes and QTL in regions under selection

Each region was investigated for genes and QTL using the Ensemble Biomart (Hubbard et al., 2009) and animal QTL Database (Zhiliang et al., 2007). It is good to compare regions of interest in *O. aris* to the corresponding areas in *B. taurus*, as the taurine genome has been better annotated. The ovine and bovine sequences were obtained from the ovine Genome browser (http://www.livestockge-nomics.csiro.au/sheep/oar1.0.php) and the UCSC Genome Browser on Cow Oct. 2007 (http://genome.ucsc.edu/), respectively. Also, two QTL databases available online including http://www.animal-genome.org/QTLdb/sheep.html and http://www.ani-malgenome.org/QTLdb/cattle.html were explored to identify any overlapping of the candidate regions with published QTL in sheep, dairy and beef cattle.

Results

Quality control

Australian Merino sheep (3974) were genotyped using the 48599 SNPs on the Illumina OvineSNP50 Bead chip. A number of 157 out of the 3974 individuals had MIND > 0.05, 259 markers were not in Hardy-Weinberg equilibrium (p < 1×10^{-6}), 2788 SNPs failed messiness test (GENO > 0.05) and 262 SNPs had MAF < 0.01 for the whole dataset. Accordingly, 45290 SNPs from 3817 individual were used for further analyses.

Population structure

Understanding the relationships between and within populations is an important step to find the relevant conservation strategies. The results derived from PCA, pairwise Weir and Cockerham's F_{ST} (WCF$_{ST}$) and NJ tree were used to explore the genetic closeness among the flocks.

The PCA results showed the investigated flocks were almost genetically close to each other except the SG2 flock that was clustered separately (Figure 1). In addition, the results indicated that there were close relationships between CRC and SG flocks which can be due to the use of common sires among the flocks. The proportion of total variation explained by first and second principal components, were 46.6 and 6.3%, respectively.
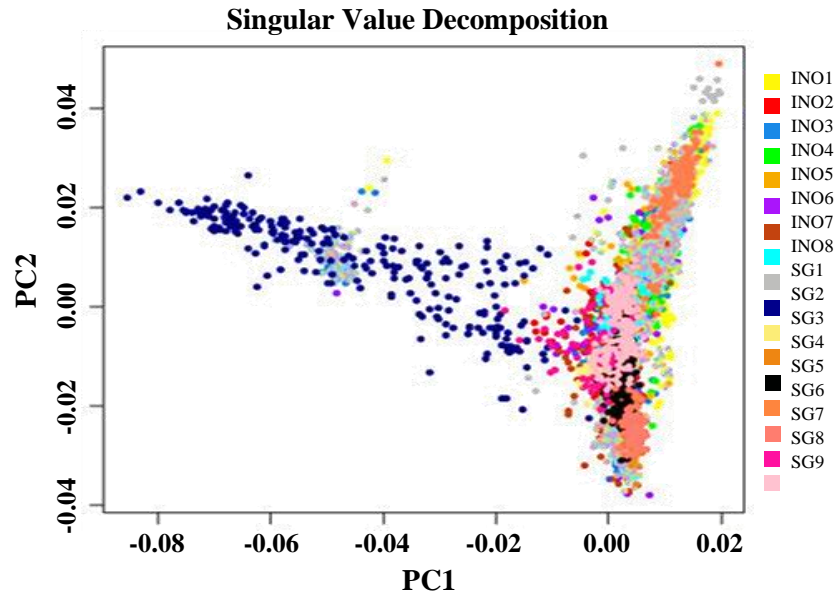
Singular Value Decomposition

Figure 1. Principal components analysis for the genetic differentiations among the Australian Merino sheep flocks.
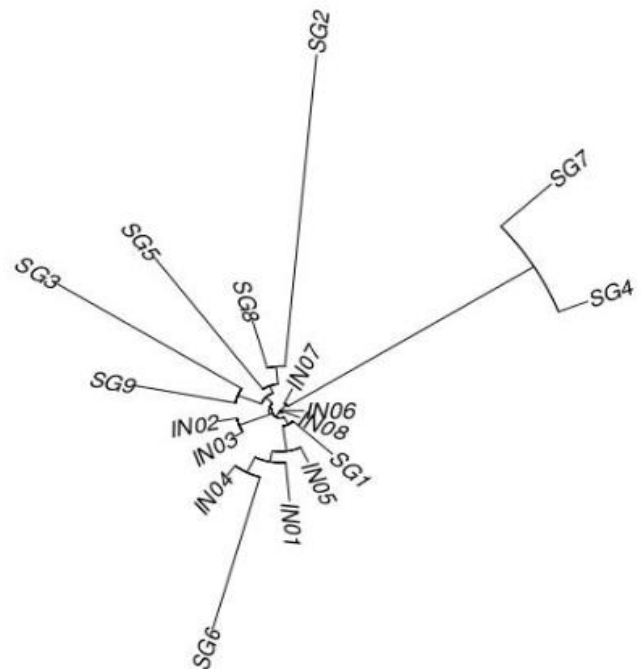
The WCF$_{ST}$ between pairs of populations was investigated to create the NJ tree (Figure 2). The lowest average pairwise WCF$_{ST}$ was observed between INO3 and INO2 flocks (WCF$_{ST}$= 0.0029), which were the most closely related pair and the next lowest pairwise WCF$_{ST}$ (WCF$_{ST}$ = 0.0046) was observed between the INO8 and INO6 flocks. The highest average pairwise WCF$_{ST}$ was observed between SG1 and SG6 flocks (WCF$_{ST}$= 0.0814). Four subpopulations were originated

from the same branch with a very close relationship (Figure 2). The shortest branch was observed for INO8 flock; while the longest one was found for SG2 where this flock had the most genetic distance with the other flocks.

Genomic distribution of F$_{ST}$

The number of individuals within each flock were not

Figure 2. Relationship between populations based on Neighbor network obtained using pair-wise estimates of Weir annd Cockerham's F$_{ST}$.

balanced and the windowed Weir and Cockerham's F_{ST} values were lowly correlated with Wright's F_{ST} values (r = 0.17). Therefore, the level of differentiations between the Australian Merino sheep was measured by unbiased estimates of fixation index (Weir and Cockerham, 1984). Several ovine genomic regions with high Weir and Cockerham's F_{ST} values were detected (Figure 3).

Based on previous studies 0.1 % of the highest theta values were considered for representing the signatures of selection (Kijas et al., 2009; Moradi et al., 2012; Yang et al., 2014). Accordingly, a theta value of 0.15 was used as a threshold for significant selection sweeps. Then, seven regions on chromosomes 2 (between 47,826,988-48,037,659 bp and; between 252,253,005-252,420,321 bp), 3 (between 85,499,961-85,588,448 bp), 6 (between 40,277,406-40,496,376 bp), 7 (between

64,875,191-65,066,014 bp), 16 (between 15,056,887-15,286,536 bp) and 26 (between 20,194,616-20,333,552 bp) were detected as the signatures of selection (Figure 3). The mean genomic WIN5theta value across all SNPs was equal to 0.032 (ranged from -0.147 to 0.317). The theta values of 6.4% of the loci (2942 SNPs) were ≤ 0. In general, F_{ST} value is varied between 0 and 1 (Wright, 1951). However, estimating a negative value is possible while it is unbiased (Akey et al., 2002).

Ovine genes and published QTL in the detected regions

A summary of published ovine genes and QTL in the regions under selection is presented in Table 1. A few candidate genes were found in these regions based on Ovine
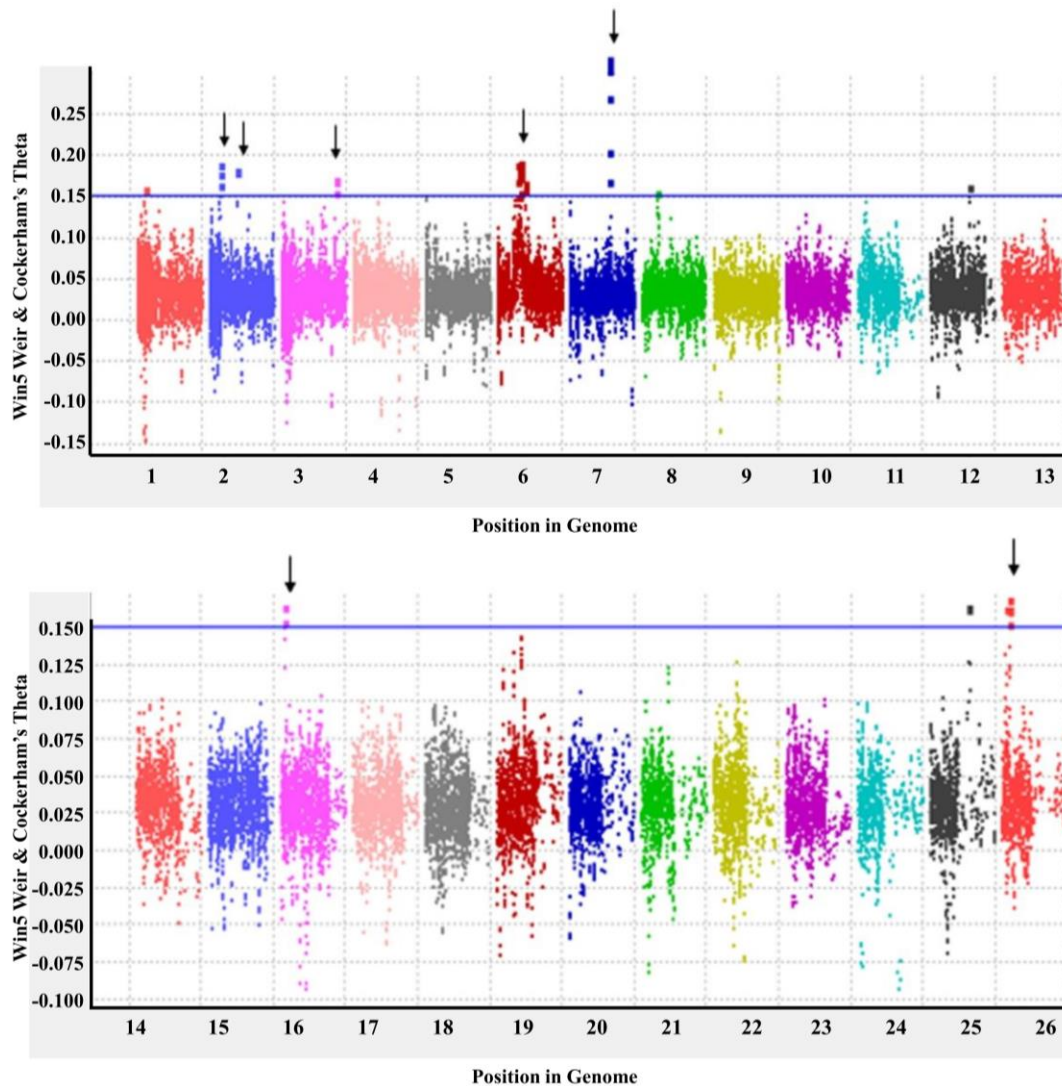

Figure 3. Distribution of windowed theta values for Australian Merino sheep by chromosome. Regions with arrows above had windowed F_{ST} values > 0.15

Table 1. Ovine genes and published QTL in regions showing evidence of selection in Australian Merino sheep data set

Location on Ovine genome	Location on Bovine genome	Gene	QTL	QTL Reference
2:47826988-48037659	8:67242625-67309081	-	Meat linolenic acid content	Karamichou et al. (2006)
			Meat arachidonic acid content	Karamichou et al. (2006)
			Meat docosapentaenoic acid content	Karamichou et al. (2006)
			Meat eicosapentaenoic acid content	Karamichou et al. (2006)
			Body weight (slaughter)	Walling et al. (2004)
			Milk fat percentage	Arranz and Gutiérrez-Gil (2012)
			Scrotal circumference	Esmailizadeh (2015)
2:252253005-252420321	-	-	Meat linolenic acid content	Karamichou et al. (2006)
			Meat arachidonic acid content	Karamichou et al. (2006)
			Meat docosapentaenoic acid content	Karamichou et al. (2006)
			Meat eicosapentaenoic acid content	Karamichou et al. (2006)
			Milk fat percentage	Arranz and Gutiérrez-Gil (2012)
3:85499961-85638700	11:22147167-2185456	hnRNPLL	Staple Length	Ponz et al. (2001)
			internal fat amount	Cavanagh et al. (2010)
			Meat conjugated linoleic acid content	Karamichou et al. (2006)
6:40277406-40496376	6:41531345-41577486	KCNIp4	Hot carcass weight	Cavanagh et al. (2010)
			Body weight (slaughter)	Hawlader et al. (2015)
			Facial eczema susceptibility	Duncan et al. (2007)
			Fecal egg count Weight at puberty	Pollot and Greeff (2004) Esmailizadeh (2015)
7:64875191-65074155	10:69614505-69635497	KTN1	Staple Length	Ponz et al. (2001)
			Fiber diameter coefficient of variance	Ponz et al. (2001)
16:15056887-15286536	20:16441192-16460717	PNF180	Body weight (slaughter)	Cavanagh et al. (2010)
			Lean meat yield percentage	Cavanagh et al. (2010)
			Subcutaneous fat area	Cavanagh et al. (2010)
			Subcutaneous fat thickness	Cavanagh et al. (2010)
26:20333552-20333552	27:23167114-23176434	TUSC3	Average daily gain	Cavanagh et al. (2010)
			Worm count	Marshall et al. (2013)
			Eggs per worm	Marshall et al. (2013)
			Change in hematocrit	Marshall et al. (2013)

Genome v3.1 Assembly. Five functional candidate genes including *hnRNPLL* (θ value= 0.171), *KCNIp4* (θ value=0.185), *KTN1* (θ value= 0.317), *PNF180* (θ value= 0.163) and *TUSC3* (θ value= 0.168) were mapped to the highest theta values. These genes were located on chromosomes 3, 6, 7, 16 and 26, respectively. However, the two detected significant regions on chromosome 2 were not linked with any of the candidate genes.

Study of the reported QTL in these regions of the ovine genome showed that they were associated with QTL of economically important traits such as meat, carcass yield, growth and wool traits. For example, the regions on chromosomes 3 and 7 are associated with QTL reported for staple length, on chromosome 26 with average daily gain and on chromosome 6 with hot carcass weight. The regions showing signature of selection in the *O. aries* genome were also compared to the orthologous areas in *B. taurus* (data not shown). The online databases of published QTL in beef and dairy cattle showed that the regions detected in the current study were associated with the QTL affecting milk yield and milk composition, body weight, udder depth and strength (Hiendleder et al., 2003; Ashwell et al., 2005; Chen et al., 2006).

Discussion

In this study, population structure of seventeen Australian Merino flocks was analyzed. The PCA results showedclose relationships among these flocks. Based on the PCA analyses, significant genetic diversity was observed among cattle and pig individuals from diverse geographical places (Gibbs et al., 2009; Yang et al., 2014). The results derived from the NJ graph and the WCF$_{ST}$ were in agreement with the PCA analysis. NeighborNet graph between different sheep breeds showed branches with nearly equal length, suggesting the approach is robust to differences in effective population size and genetic drift between populations (Kijas et al., 2012).

In current study, a mean theta value of 0.032 was found for the genetic differentiation between the flocks investigated. Kijas et al. (2009) reported a value of 0.023 when 23 domestic breeds and two wild sheep species were used. They indicated that the low differentiation among sheep breeds was due to their short evolutionary history. The results are in agreement with those derived from a study conducted by Moradi et al. (2012) where a mean value of 0.024 was calculated for the genetic differentiation between two Iranian sheep breed including Zel and Lori Bakhtiari. In our study, the highest theta value (0.372) was found for chromosome 7. Artificial selection and local environmental adaptation can change the allelic frequencies of specific loci, then the frequency of useful alleles at the selected loci will increase, leading to a higher than expected level of population differentiation (Akey et al., 2002).

Genetic improvement for wool and meat characteristics as well as disease resistance has been the main breeding objective in Merino sheep breeding programs. In the investigated Merino flocks, the region between 40.27 and 40.49 Mb on OAR6 was associated with hot carcass weight and body weight at slaughter age. The QTL underlying weight at puberty in ewe lambs in Kermani sheep was reported on chromosome 6 at 47 cM (Esmailizadeh, 2015). This region was also associated with body weight at mature age, gestation length, milk yield, milk fat yield, and milk fat percentage in a 41.5 Mb interval on BTA6 (Chen et al., 2006; Maltecca et al., 2008; McClure et al., 2010). The biologically relevant gene in this region, KCNIP4 (Kv channel-interacting protein 4), plays a crucial role in a variety of growth processes, including body weight and growth regulation. According to previous studies, the most significant SNPs which impact on body weight were on chromosomes 6 (position OAR6_41936490.1). This region was linked with several candidate genes such as *KCNIP4*, *GPR125* (G protein-coupled receptor 125) and *GBA3* (glucosidase beta acid 3) (Hawlader et al., 2015). In other studies in the chicken, the *KCNIP4* and *GPR125* genes were associated with body weight and growth rate from 6 to 12 weeks of age (Gu et al., 2011; Jin et al., 2015).

Another important candidate gene under selection was Kinectin-1 (*KTN1*). This gene was located on OAR7_ 65066014 (theta= 0.372). The *KTN1* encodes kinectin in the endoplasmic reticulum and is responsible for the transport of vesicles along microtubules (Hibar et al., 2015). The *IGF* (Insulin-Like Growth Factor) gene can be activated by *RhoA* indirectly. Upon *RhoA* is also activated by *KTN1* (Tran et al., 2002; Bai et al., 2006); and *IGF-II* is required for normal placental (De-

(DeChiara et al., 1990). Furthermore, *IGF-I* was associated with several reproductive traits, such as twin ovulations (Echternkamp et al., 2004), age at first calving (Brickell et al., 2007), pregnancy rate to first service (Patton et al., 2007), and preimplantation embryonic development (Velazquez et al., 2005). The studies of eQTL from 304 individuals from the North American brain expression cohort showed evidence of altering the expression of the *KTN1* gene in both the brain and blood tissue (Hibar et al., 2015).

The locus with the highest theta value, located on chromosome 7, was associated with the staple length and coefficient of variation of fiber diameter (CVFD) which are important economic traits in Merino sheep. A moderate negative genetic correlation was reported between CVFD and litter size (- 0.33 ± 0.04) and between CVFD and yearling weight (-0.22 ± 0.04) in Australian Merino sheep (Asadi Fozi et al., 2005). Meat production is affected by both the litter size and body weight. Litter size, the main fertility trait in sheep, is of high economic value (Notter, 2008), only expressed in one sex, cannot be recorded at an early ages, and has low heritability. Therefore, low genetic gain can be achieved for litter size when animals are selected based on this trait performance. Accordingly, the region detected herein can be useful for genetic improvement of litter size, yearling weight as well as staple length and CVFD.

The regions on chromosomes 2, 6 and 16 were associated with body weight at slaughter age. Previous studies showed moderate genetic correlation (0.24–0.39) between body weight at slaughter age and reproduction traits such as fertility and litter size (Safari et al., 2007). Kijas et al. (2012) also reported that a region on chromosome 16 that was associated with growth traits in sheep. In their study a genome wide scan was performed using 2819 individuals from 74 sheep breeds including the Merino.

Conclusions

Identifying recent positive selection signatures in domesticated animals can provide information on genomic regions that are affected by selection. It can be useful to explore the advantage of mutations and important biological pathways for economically important traits. In summary, we revealed the genetic differentiation among Australian Merino sheep flocks using the Illumina OvineSNP50 BeadChip. The PCA results did not show a clear differentiation among the selected populations. Genome wide analysis of selection signatures detected 7 regions under selection. These regions were almost associated with QTLs that have effects on growth, carcass,

reproduction, and wool traits in sheep, beef and dairy cattle. These are important traits for the Australian Merino sheep industry. The results may be used in Merino breeding programs. In addition, the genetic diversity among Merino flocks can be explored.

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کاوش ژنومیک برای شناسایی نواحی تحت انتخاب گوسفندان مرینوس استرالیائی

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چکیده   انتخاب و اهلی کردن پروسه‌هایی هستند که الگوهای تنوع ژنتیکی را در داخل و بین جمعیت‌ها تغییر می‌دهند. شناخت اساس ژنتیکی تنوع فنوتیپی، یکی از اهداف اصلی تحقیقات زیستی است و استفاده از حیوانات اهلی ابزاری سودمند برای پیشرفت در راستای این هدف می‌باشد. یک روش برای کشف نواحی تحت انتخاب مقایسه ارزش‌های F_{ST} بین جایگاه‌ها است. در این مطالعه، کاوش ژنومی با ۵۰۰۰۰ نشانگر تک نوکلئوتیدی به منظور شناسایی نواحی تحت انتخاب گوسفند مرینوس استرالیائی (۸ گله CRC و ۹ گله SG) صورت گرفت. به منظور بررسی نشانه‌های انتخاب از روش برآوردگر ناریب F_{ST} (تتا) استفاده شد. در مجموع هفت ناحیه از ژنوم که نشانگرهای SNP آنها بالاتر از ۰/۱ درصد حد بالای توزیع تجربی تتا بودند، به عنوان نشانه‌های انتخاب در مقایسه گله‌های مرینوس استرالیایی شناسایی شده و مورد بررسی‌های بیشتر قرار گرفتند. این مناطق با ارزش ناریب شاخص تثبیت (تتا) بالای ۰/۱۵، روی کروموزوم‌های ۲ (دو ناحیه)، ۳، ۶، ۷، ۱۶ و ۲۶ واقع شده‌اند. در این مطالعه تعدادی ژن کاندیدا مهم مرتبط با صفات تولید مثل و رشد شناسایی شد. در نهایت بررسی QTLهای گزارش شده نشان داد که این مناطق با QTLهای صفات مهم اقتصادی از جمله صفات مرتبط با تولید مثل، لاشه، رشد و پشم در ارتباط می‌باشند. مطالعه بیشتر این نواحی در شناسایی ژن‌های کاندید برای صفات مهم اقتصادی در نژادهای گوسفند موثر خواهد بود. همچنین از اطلاعات این تحقیق می‌توان برای فهم بهتر تنوع ژنتیکی این نژاد استفاده نمود.