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Genome-wide association study (GWAS) of high productivity classes in the Karachaevsky sheep breed

Alexander Krivoruchko (✉), Olesya Yatsyk, Anastasiya Kanibolockaya, Valery Kulintsev

North Caucasus Federal Agrarian Research Centre, All-Russian Science Research Institute of Sheep and Goat, Stavropol, Russian Federation

✉ Corresponding author: rcvm@yandex.ru

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ABSTRACT

Using the Illumina Ovine Infinium HD BeadChip 600K DNA array, we performed a genome-wide association study (GWAS) in Karachaevsky breed sheep with different class evaluations (elite and super-elite). The classification was carried out according to complex criteria, including live weight, the presence of horns, colour and length of the coat, and body size. Fifteen single nucleotide polymorphisms (SNPs) were detected, the frequency of occurrence of which reliably depends on the individual belonging to the assessed class groups. The search for candidate genes near to these SNPs allowed us to divide them into several groups. Five SNPs are in the introns of genes, four are in the exons, two are associated with genes encoding long non-coding RNAs, and the rest are intergenic variants. Most of the detected candidate genes are associated with the processes of growth and development of the body. The most significant differences in the frequency of occurrence were shown by the SNPs rs427394436, rs429383103, rs398161871 and rs421966191 ($p = 1.022 \times 10^{-14}$) located on chromosomes 1, 2 and 21. As new candidate genes, we proposed: *MAEL*, *EPHA4*, *CPT1*, *FCER1A*, *CWC27*, *SHISAL2B*, *SCIN*, *MYO16* and *ITPKB*. In addition, SNPs with a significant difference in the frequency of occurrence can be used as molecular genetic markers when conducting breeding work in sheep of the Karachaevsky breed.

Keywords: sheep, genome-wide association study, GWAS, SNP, Karachaevsky breed

INTRODUCTION

Genome analysis as a way of assessing and predicting the productive qualities of animals is a current trend in breeding in the development of livestock worldwide (Fahar et al., 2017). The study of gene structure is related to the implementation of economically valuable phenotypic traits and is carried out in all countries with an average level of agricultural development (Georges et al., 2019). The revealed genomic features are mostly single nucleotide polymorphisms (SNPs) that either change the structure of the encoded protein due to codon substitution or are inherited in linkage with different alleles of the target gene. This makes it possible to use the detected SNPs as molecular markers for selective assessment of the prospects of using a particular animal in breeding (Meuwissen et al., 2016).

Genes whose localisation on a chromosome is associated with a particular phenotype are classified as candidate genes. To detect them in the genome using a genome-wide association study (GWAS), individual SNPs with the desired trait deposited on a DNA beadchip is used (Sahu et al., 2017; Abdoli et al., 2018). Both individual phenotype parameters that determine the productivity of the animal and their combinations are included in the mathematical models used to estimate the quality of each animal under study. The latter method is usually used in the presence of data on the development of animals in different conditions, to eliminate the influence of external factors not related to the genotype (Benavides et al., 2018; Miller et al., 2018). Both methods are used in the study of genome-wide associations in sheep, but

they do not always fully satisfy the requirements for the detection of new candidate genes using the GWAS method (Kominakis et al., 2017).

Even though work to improve sheep breeds is ongoing, in any breed group animals are divided according to parameters relating to productive traits. These parameters usually show a normal distribution, in which the largest number of individuals have parameters close to the average for the breed, and a smaller number either lag behind or surpass them. The latter constitute a group of super-elite animals of the breed that are usually represented at exhibitions and are used to the maximum in breeding to improve the quality of offspring. Since the sample in this case is very small, it is advisable to use a non-quantitative "case/control" analytical approach. In such an analysis, an individual carrying a phenotypic trait of interest (belonging to the super-elite class) falls into the "case" group, and an individual not possessing the qualities of interest (elite) into the “control” group (Guomundsdottir, 2015). This enables the identification of productive indicators in sheep immediately after birth and pre-selection of parental pairs to produce offspring of high quality (Milchevskiy 2018). Genomic technologies for solving such problems are based on genome-wide scanning for many SNPs, including those associated with quantitative trait loci (QTL) (Seno et al., 2018).

Whole genome scanning is mostly performed in dairy cattle (Weller et al., 2017). The experience of use in this sector has showed that, with an increase in the volume of data obtained, the accuracy of prediction of breeding qualities significantly increases, even without the use of progeny estimation. Now abroad, very few bulls are used for breeding without a genomic evaluation, which is mandatory for the sale of breeding stock.

Unfortunately, in sheep, the use of modern molecular genetic methods is still far behind the level seen in cattle. This is due to the comparatively wide variety of sheep breeds. Moreover, individual sheep breeds can vary greatly in phenotype, and breed groups include only a few thousand individuals, which is not sufficient for full genomic selection. In addition, the peculiarities of keeping sheep in various pastures make it difficult to standardise the assessment of productive qualities, which often depend heavily on the food supply. However, several tests for individual polymorphisms are used in sheep breeding; for example, those in the genes encoding calpastatin and myostatin, whose influence on the quality of meat products has been shown (Hope et al., 2013; Palmer et al., 2000). These methods are no longer limited to scientific research and are used in commercial sheep farming (Julius 2007). However, the use of marker selection for polymorphisms associated with these genes has already been exhausted in many respects. The positive alleles in the breeds are fixed in the form of homozygotes and there is no place to wait for the influx of negative alleles inside the breed (Kijas et al., 2007). In this regard, research aimed at identifying new markers of economically valuable traits of sheep using GWAS tools is becoming increasingly important (Gebreselassie et al., 2019). Recent studies have identified loci associated with reproductive qualities (Abdoli et al., 2019; Smołucha et al., 2021), wool (Zhao et al., 2021) and milk productivity (Li et al., 2020; Sutera et al., 2021), and resistance to parasitic diseases (Ahbara et al., 2021) and congenital anomalies (Mastrangelo et al., 2018; Hirter et al., 2020). Particular attention has been paid to the search for loci associated with meat productivity and body size (Lu et al., 2020; Almasi et al., 2021; Jiang et al., 2021).

Breeds that have existed in isolation for a long time in a limited geographical area are of great interest in the search for new candidate genes. These include the Karachaevsky sheep breed, which has been separately bred in the North Caucasus since the 19th century. Animals of this breed are not large; rams weigh up to 70 kg, and ewes up to 50 kg. The breed belongs to the coarse-haired group, but is universal, as milk, meat and wool are obtained from the sheep. The breed is precocious, the meat has an excellent flavour, and the slaughter yield exceeds 50%. The output of marketable milk reaches 50 kg per lactation. Rams and ewes can produce 3 kg and 2.6 kg of wool per year, respectively. The animals are very resistant to the effects of most adverse environmental factors and infections (Tambiev 2007; Bolatchiev et al., 2012).

The aim of this study was to identify new candidate genes linked to productivity, located next to SNPs reliably associated with the classification of Karachaevsky sheep in the super-elite group.

MATERIALS AND METHODS

Ethics statement

The sample collection and study purpose were approved by the Institutional Animal Care and Use Committee (approval number 2018-0038, 20.09.2018) of the All-Russian Research Institute of Sheep and Goat Breeding, Stavropol, Russian Federation.

Phenotypic data

The highest quality 60 rams of the Karachaevsky breed at the age of 12 months were the object of this study. The rams were selected after comparative grading of the 412 rams from one herd, delivered from the ewes of the breeding core in Stavropol Krai (Russian Federation). The criteria for animals belonging to the elite class were: the presence of horns, uniform black colour, and live weight of at least 45 kg. The body must be of medium size and strong constitution, with well-developed bones. The head must be straight or slightly humped. The length of the body must be slightly greater than the height at the withers. The chest must be deep, well developed, and not wide. The limbs must be thin, dry and well set, with a strong hoof. The wool coat must consist of a long, soft, medium wavy elastic spine. The awn length must not be less than 12 cm, with no dead and dry hair. The colour of the wool coat must be uniform, with a strong sheen, and the guard hair (braids) evenly distributed throughout the body. The super-elite class included animals that outperform elite animals by at least 10%, according to the characteristics described. Class I included animals characterised mainly by the characteristics of the elite class but were smaller in size or with some defects in the quality of the wool and exterior. According to the results of the scoring, 50 rams were assigned to the elite class and marked as “controls”, and ten to the super-elite class (“cases”). The latter, as outstanding individuals, were selected in the group of exhibition animals, with only ten of them found in the studied herd. All rams were clinically healthy, kept in optimal conditions and fed with a total mixed ration.

Genotyping

Genomic DNA was isolated from whole blood samples taken under aseptic conditions from the jugular vein using the Pure Link Genomic DNA MiniKit kit (Invitrogen Life Technologies, USA) in accordance with the manufacturer's protocol. Animal genotyping was performed using Ovine Infinium HD BeadChip 600K (Illumina Inc. CA, USA) according to the manufacturer's protocol. Initial processing of the genotyping results was performed using the Genome Studio 2.0 software (Illumina Inc. CA, USA).

Quality control of genotyping

Quality control of genotyping was carried out using PLINK V.1.07 software. The data processing included samples with an indicator of the number of detected SNPs (call rate) more than 0.95. Substitutions with a minor allele frequency (MAF) of less than 0.05 and a missing genotype of more than 0.1 were also excluded. The value p = 0.0001 was used as the threshold according to the Hardy-Weinberg equilibrium criterion. With a positive result, 47 samples from the elite and 10 from the super-elite animals underwent genotyping quality control. From the 606,006 SNPs, 506,819 polymorphisms were used for further analysis.

Genetic and statistical analysis

The genome-wide association study was performed using the PLINK V.1.07 software (Purcell et al., 2007). It is based on the assessment of the significance of SNP influence on the phenotype variability from the elite and super-elite class using a basic allelic chi-square test. To confirm the significance of differences in multiple comparisons, a p-value estimate with Bonferroni correction was used. This is calculated according to base significance level, with p = 0.05 and the number of polymorphisms equal to 506,819 (0.05 / 506,819 = 0.987-7). Visualisation and graphing were performed using the “QQman” package in the programming language “R”.

The search for candidate genes was performed in the region 200,000 bp upstream and downstream of the SNPs (half of centimorgans) that showed significant differences in occurrence among animals of the studied groups. For SNP mapping and alignment, the Ovis_Aries_3.1 genome assembly was used. Gene annotations were performed using the genomic browsers UCSC (www.genome.ucsc.edu) and Ensembl (www.ensembl.org).

RESULTS

The genome-wide study for associations between the frequencies of individual SNPs in Karachaevsky sheep and the "super-elite" class showed many SNPs with a confidence exceeding $-\log_{10}(p) = 5$ (lower line in the Manhattan plot, Fig. 1, A). A quantile-quantile plot for SNPs throughout the genome confirms the data obtained (Fig. 1, B).

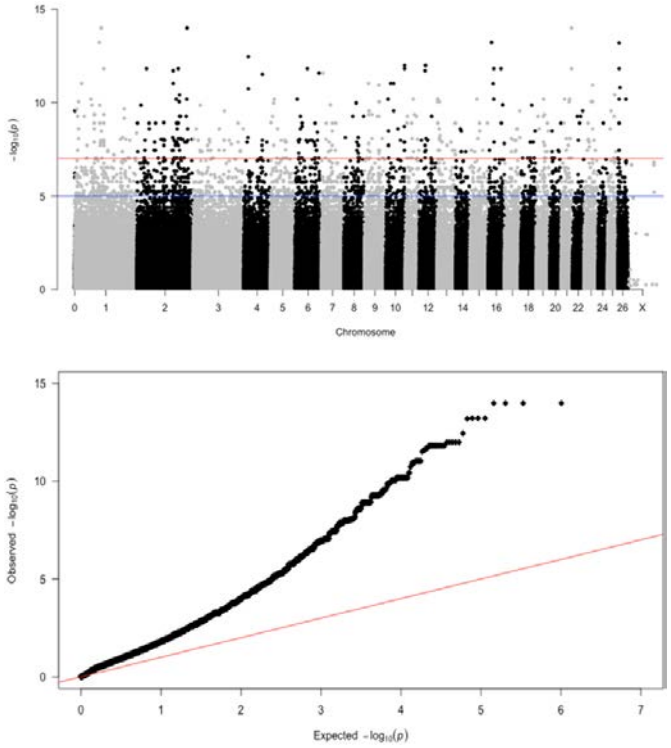

Figure 1. A) Manhattan plot of GWAS results with a set of $-\log_{10}(p)$ values for the studied SNPs. The lower line indicates the threshold of significance of differences with the value of $-\log_{10}(p) = 5$, the upper line shows the threshold of significance of differences using the Bonferroni correction with the value of $-\log_{10}(p) = 6.86$. B) QQ-plots for the probabilities of the distribution of the reliability of SNP estimates throughout the genome. Dots indicate $-\log_{10}(p)$ values for individual SNPs. The line indicates the expected values when confirming the null hypothesis of the absence of associations

Moreover, an increasing deviation from the expected theoretical distribution, coinciding with the null hypothesis, is already observed at sufficiently small values of $-\log_{10}(p)$. Values showing a significant deviation start from the level of $-\log_{10}(p) = 2$ and increase up to the maximum value for several SNPs, exceeding 14.

Due to the large number of polymorphisms that overcame the threshold value of 5 units, we tested the null hypothesis with more stringent parameters and the introduction of the Bonferroni correction. In this case, the threshold value was set at $-\log_{10}(p) = 6.86$ (the upper line in the Manhattan plot, Fig. 1, A). Using this selection criterion, the number of SNPs for which $-\log_{10}(p)$ exceeded the confidence threshold was still large. Therefore, for further study, we selected the 15 SNPs with the highest rates. These SNPs are found significantly more often ($-\log_{10}(p) > 12$) in the group of super-elite animals and are associated with high ranking and productive qualities of the Karachaevsky sheep breed.

Seven of the selected SNPs with the highest confidence indices are located on chromosomes 1, 2, 16 and 21. A more detailed analysis of the location of SNPs on chromosome 1 (Fig. 2. A) shows that two SNPs with a maximum confidence value, as well as a couple with highly reliable indicators (Fig. 2. B), are at a close distance and possibly jointly inherited. On chromosome 2, the SNP with the highest $-\log_{10}(p)$ value (rs398161871) is at the opposite end of the chromosome to the other SNP (rs400925984), which is also in our choice for next analysis (Fig. 2. C, D). On chromosome 16 (Fig. 2. E, F), the two analysed SNPs are located very close to each other; however, the SNPs with lower reliability are located at a greater distance from this pair. Chromosome 21 also contains two polymorphisms with high indices, located in the same chromatid region (Fig. 2. G, H), but one of them was not included in our analysis, since it had a lower $-\log_{10}(p)$ value than the 15 we selected.

Among the selected SNPs, five were in introns (four in the same intron of one gene), and four in exons (Table 1.). Two polymorphisms belonged to genes encoding long non-coding RNAs with unexplained functions.

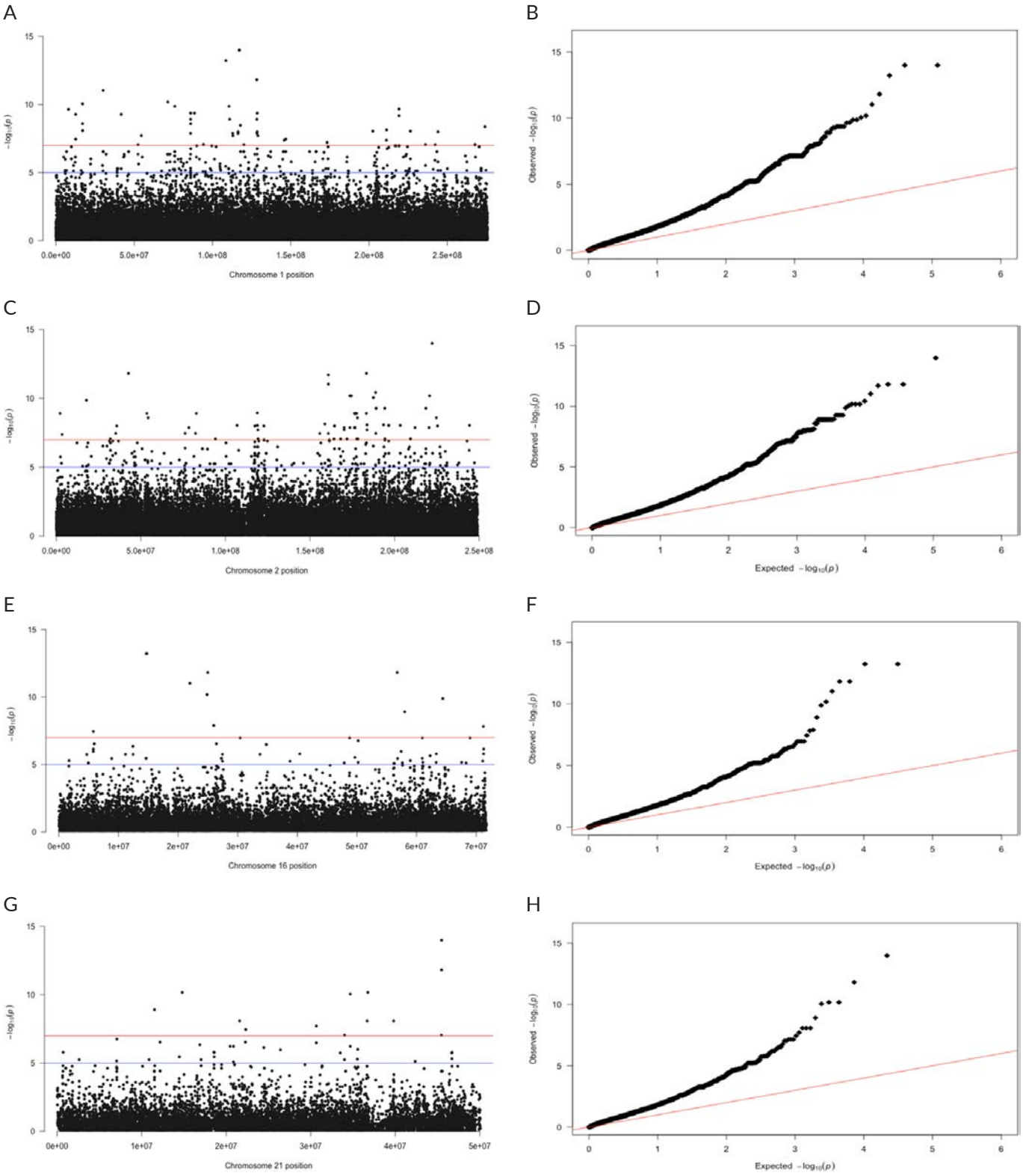

Figure 2. A, C, E, G) Manhattan plots of GWAS results with a set of -$\log_{10}$ (p) values of the studied SNPs at individual loci of chromosomes 1, 2, 16 and 21. The lower line indicates the threshold of significance of differences with the value of -$\log_{10}$ (p) = 5, the upper line indicates the threshold of significance of differences using the Bonferroni correction with the value of -$\log_{10}$ (p) = 6.86. B, D, E, H) QQ-plots for the probability distribution of the reliability SNP estimates localized on chromosomes 1, 2, 16, and 21. Dots indicate -$\log_{10}$ (p) values for individual SNPs. The line indicates the expected values when confirming the null hypothesis of the absence of associations

Table 1. Parameters of SNPs with the highest associations with a super-elite phenotype of sheep. A1 - minor allele; A2 - main allele; F_A - frequency of the minor allele in the super-elite animal group; F_U - frequency of the minor allele in the elite group

No.	SNP	Chromosome/ Position	A1	A2	F_A	F_U	P	Gene / Distance to the gene
1.	rs427394436	1/117134325	C	A	0.6	0	1.022E-14	*MAEL*/ intron 8-9
2.	s429383103	1/117151905	G	A	0.6	0	1.022E-14	*MAEL*/8371 bp
3.	rs398161871	2/222206719	G	A	0.6	0	1.022E-14	*EPHA4*/308103 bp
4.	rs421966191	21/45480831	G	A	0.6	0	1.022E-14	*CPT1A*/ exon 3
5.	rs413143573	1/108572977	A	G	0.8	0.03	5.98E-14	*FCER1A*/ exon 3
6.	rs418585313	16/14664207	A	G	0.8	0.03	5.98E-14	*CWC27*/ exon 10
7.	rs423862473	16/14773850	A	G	0.8	0.03	5.98E-14	*SHISAL2B*/ exon 1
8.	rs422928596	4/20730824	G	A	1.0	0.08	3.58E-13	*SCIN*/ 11906 bp
9.	rs416509643	10/83680802	A	G	0.8	0.04	1.02E-12	*MYO16*/ 16845 bp
10.	rs418210189	12/27831588	G	A	0.8	0.04	1.02E-12	*ITPKB*/ intron 4-5
11.	rs409520957	12/27831923	G	A	0.8	0.04	1.02E-12	*ITPKB*/ intron 4-5
12.	rs416320917	12/27847768	A	G	0.8	0.04	1.02E-12	*ITPKB*/ intron 4-5
13.	rs160764666	12/27859119	A	G	0.8	0.04	1.02E-12	*ITPKB*/ intron 4-5
14.	rs400925984	2/160837722	G	A	1.0	0.09	1.99E-12	*lincRNA*/186476 bp
15.	rs430227344	12/26043493	A	G	1.0	0.09	1.99E-12	*lincRNA*/4 312 bp

One was located next to the RNA gene, the second was located almost 200,000 bp from the gene. Intergenic SNPs were detected no further than 17,000 bp from protein coding genes. Four SNPs (two on chromosome 1 and two on chromosome 2) differed in that they were not found in the group of elite animals and were present in 60% of haplotypes in individuals from the super-elite category. Three SNPs were detected in all super-elite animals, and in the comparison group the frequency of mutant haplotypes did not exceed 9%.

DISCUSSION

Of the four SNPs that showed the most significant differences in the frequency of occurrence between animals of the elite and super-elite groups, two are located on chromosome 1. These SNPs are detected in the region of the *MAEL* gene, which encodes the maelstrom spermatogenic transposon silencer. Its function is to repress mobile genetic elements in germ cells during spermatogenesis (Klattenhoff and Theurkauf, 2008). Moreover, it actively interacts with several regulatory RNAs, and its knockout leads to DNA damage and disruption of meiosis (Costa et al., 2006). Until now, the effect of *MAEL* gene polymorphism on the productive qualities of farm animals has not been studied. Considering the complete absence of the mutant allele of the SNP in the elite group of animals and its presence only in rams of the super-elite group, the *MAEL* gene can be considered a candidate gene that affects the phenotype of the Karachaevsky sheep breed.

The SNP rs398161871 is located in an intergenic DNA segment on chromosome 2. It is reasonably far from the nearest gene, *EPHA4*, which encodes EPH receptor A4. The protein product of this gene belongs to the estrin receptors from the protein tyrosine kinase group and is involved in several development processes as a key mediator of maintaining tissue homeostasis (Darling and Lamb, 2019). We cannot exclude that the locus

variability we discovered is determined by polymorphism of this gene. However, it is also possible that there are undescribed regulatory elements in the intergenic space that are inherited in conjunction with the studied SNP. In any case, further closer examination of the rs398161871 locus is required to identify the structural features of the DNA that affect the productive qualities of these sheep.

The rs421966191 SNP located on chromosome 21 is a missense variant. It is located in exon 3 of the *CPT1A* gene, which encodes carnitine palmitoyltransferase 1A, a key enzyme necessary for the transport of long fatty acids into the mitochondria (McGarry and Brown, 1997). The relationship of polymorphisms in this gene with productivity parameters in animals has not been studied. In humans, changes in the structure of this gene are accompanied with several pathologies, including death in childhood (Fohrer et al., 2017). Considering the importance of the *CPT1A* gene for the metabolism of organs and tissues, it is an important candidate gene, the effect of which on animal productivity should be studied in more detail.

In the exon region of the *FCER1A* gene located on chromosome 1, there is a SNP rs413143573, described as a missense variant. The gene *FCER1A* encodes receptor Ia of the Fc fragment of immunoglobulin E. This high-affinity receptor provides interaction with immunoglobulin E loaded antigen in the development of immune hypersensitivity reactions (Messingham et al., 2014). The effect of the *FCER1A* gene on the productive qualities of animals has not been studied. However, its important role in the immune response indicates a possible connection with the development of the organism and makes it possible to classify candidate genes.

On chromosome 16, there are two SNPs with a highly reliable difference in the frequency of occurrence within the group of super-elite Karachaevsky sheep. The first SNP, rs418585313, is located in an exon of the *CWC27* gene, which encodes spliceosome associated cyclophilin. In the presence of this SNP, the amino acid alanine is replaced by valine. The protein product of this gene is an isomerase involved in the formation of spliceosomes, found in all mammalian cells (Adams et al., 2015). Thus, the variant rs418585313 affects the processes of translation and conformation, which, at the level of the organism, may manifest as a phenotypic change. Therefore, the *CWC27* gene is a promising candidate associated with the productive qualities of sheep.

The second SNP on chromosome 16, rs423862473, is located in an exon of the *SHISAL2B* gene. The protein product of this gene belongs to a group of regulators of head development during embryonic development in vertebrates. This function is mediated by interaction with the growth factors FGF and Wnt (Yamamoto et al., 2005). The presence of this SNP leads to the replacement of aspartic acid with asparagine. A change in the structure of the peptide indicates possible consequences in the form of an effect on the interaction with growth factors, not only in the embryonic period, but also in ontogenesis as a whole. Thus, the *SHISAL2B* gene can be considered as a candidate gene that affects the growth and development of sheep.

Next to the *SCIN* gene encoding scinderin is the SNP rs422928596. Unusually, in our study, this SNP was found in all animals from the super-elite group; in the elite group it was found in only 8% of individuals. The scinderin protein gene is a promising candidate gene, which primarily affects meat productivity. This protein belongs to the group of actin-binding proteins. Actin is involved not only in muscle contraction, but also in the processes of cell migration, proliferation, and differentiation (Lejen et al., 2002; Jian et al., 2018).

Another promising candidate gene associated with productive qualities is *MYO16*, which encodes the myosin XVI protein. This myosin isoform is characterised by increased expression in the nervous tissue and is involved in the regulation of cytoskeleton function (Kengyel et al., 2015). Next to the *MYO16* gene is the SNP rs416509643, found in almost all members of the super-elite group of Karachaevsky sheep and in only 4% of the remaining animals.

A group of four SNPs with a significant relationship with productivity is localised in an intron of the *ITPKB* gene,

which encodes inositol-triphosphate 3-kinase isoform B. This enzyme is involved in energy metabolism (Pattni and Banting, 2004) and affects the function of several somatic cells, including those of the immune system (Sauer et al., 2013). Given the number of SNPs located within the *ITPKB* gene and its functional significance, we consider it one of the most promising candidate genes that affects productive traits.

Two SNPs, rs400925984 and rs430227344, are located next to genes encoding long non-coding RNAs. The function of these RNAs has not yet been studied. In general, long non-coding RNAs are involved in many processes, acting as regulatory molecules (Ulitsky and Bartel, 2013). This function does not extend only to interactions with DNA; the work of intracellular systems in the cytoplasm is also subject to their regulation (Rashid et al., 2016). Even though these sequences are not protein-coding genes, it is possible to consider them as potential candidate genes whose function is associated with the manifestation of phenotypic characteristics in animals.

CONCLUSIONS

This GWAS conducted in the Karachaevsky sheep breed made it possible to detect several SNPs associated with productive qualities of animals belonging to the super-elite group. These SNPs are located in various areas of the genome near or within genes. Most of these genes are involved in the growth and development of the animals. Based on this study, we propose to consider these genes as potential candidates for influencing the productive parameters of sheep. We recommend a more detailed study of these genes in order to detect specific structural features that change the function of their protein product. The identified SNPs can be used as genetic markers in marker-assisted selection to increase the productivity of the Karachaevsky sheep breed.

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