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A STUDY OF GENETIC MECHANISMS UNDERLYING THE FAT TAIL PHENOTYPE IN SHEEP: METHODOLOGICAL APPROACHES AND IDENTIFIED CANDIDATE GENES

(review)

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Abstract

Fat-tailed sheep breeds comprise 25 % of the global sheep population and are widely distributed in Africa, Asia (A. Davidson, 1999), the Middle East (S.P. Alves et al., 2013), as well as in Russia (I.M. Dunin et al., 2013). The fat-tailed sheep breeds were valued since their fat was an important ingredient of national cuisine in many ethnic groups (C. Perry, 1995; A. Hajihosseinlo et al., 2015). To-date the customers prefer lean food and cut down the fat intake, and therefore the benefits of large fat tails of sheep have reduced their importance for food production (A. Nejati-Javaremi et al., 2007; M. Moradi et al., 2012). The development of genomic editing technologies (N.A. Zinovieva et al., 2019) makes it relevant to search for genes that determine the "fat tail" phenotype for the subsequent knockout without side effects on other valuable traits of the fat-tailed sheep breeds. This review summarizes the results of studies on identification of candidate genes associated with fat tail trait. Various methods are used to identify candidate genes, including search for selective sweeps (signatures of selection) based on the calculation of differences in allele frequencies (F_{st} values) or haplotypes frequencies between populations (hapFLK method) (M.H. Moradi et al., 2012; M.I. Fariello et al., 2013; C.M. Rochus et al., 2018); genome-wide association studies (GWAS) that require an availability of a phenotypic variability base for the studied traits of economic importance (S.S. Xu et al., 2017); analysis of copy number variation (CNV) that can alter gene expression due to deletion or duplication of genes in the regions of variation (C. Zhu et al., 2016; Q. Ma et al., 2017; V. Bhanuprakash et al., 2018); study of gene expression using RNA-seq technology based on transcriptome analysis using new generation sequencing technology (NGS) (W.A. Hoeijmakers, 2013). Summarizing the research results, the most significant candidate genes associated with the fat deposition of the tail of sheep are *BMP2* and *VRTN* (Z. Yuan et al., 2017; S. Mastrangelo et al., 2018; Z. Pan et al., 2019); *PDGFD* (C. Wei et al., 2015; S. Mastrangelo et al., 2018); genes of the *Homeobox* family (D. Kang et al., 2017; A.A. Yurchenko et al., 2019; A. Ahbara et al., 2019); *SP9* (Z. Yuan et al., 2017; D. Kang et al., 2017); *WDR92* and *ETAA1* (Z. Yuan et al., 2017; L. Ma et al., 2018); *CREB1* (S.S. Xu et al., 2017; L. Ma et al., 2018); *FABP4* (M.R. Bakhtiarizadeh et al., 2013; B. Li et al., 2018); *PPARA*, *RXRA*, *KLF11, ADD1, FASN, PPP1CA* and *PDGFA* (C. Zhu et al., 2016; Q. Ma et al., 2017). To search for candidate genes involved in the formation of a fat tail phenotype in the Russian sheep breeds a QTL mapping resource sheep population was established by crossing the long-fat-tailed Karachaev and the short-thin-tailed Romanov breeds, to perform a genome-wide association study.

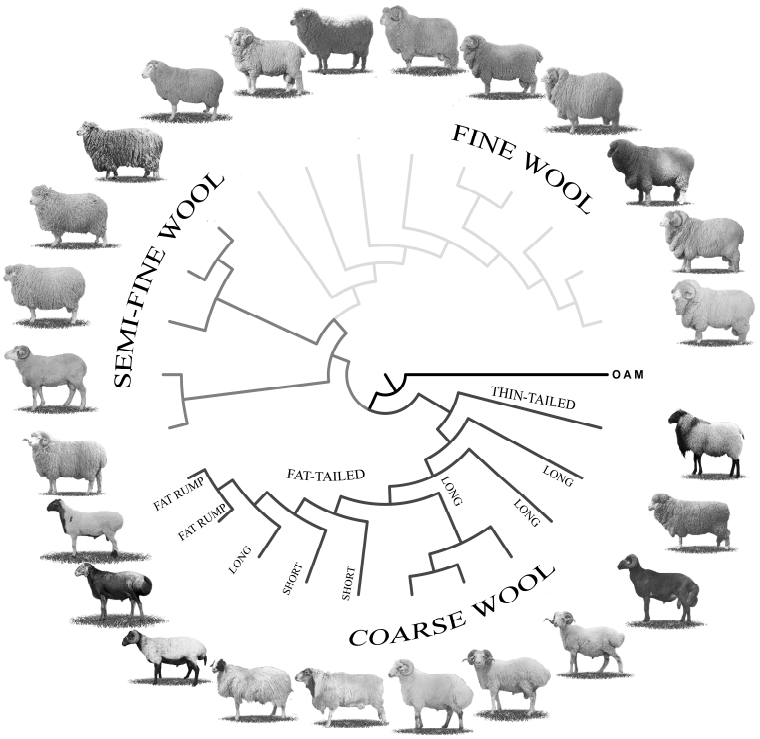
Keywords: domestic sheep, fat tail, fat rump, genetic marker, SNP, DNA chips, RNA-seq, GWAS, CNV.

The identification of genes underlying economically significant phenotypes can indicate potential targets for marker-assisted and genomic selection, as well as genomic editing, making gene identification a necessary basis for the development of genetic technologies in animal husbandry [1].

Significant changes in human dietary requirements, including an increased demand for lean food [2], lead to important changes in the goals of breeding for a few livestock species, including sheep. Fat-tailed and fat-rumped sheep constitute 25% of the global sheep population and are widespread in the countries of North Africa, Asia [3, 4] and the Middle East [5], as well as in Russia [12] of the 15 semicoarse wool and coarse wool sheep breeds in Russia are fat-tailed or fat-rumped [6].

The predominance of these breeds is because, for a long time, fat from the fat rumps of sheep was an important ingredient in national cuisine [7, 8]. Currently, among people worldwide, including ethnic groups in southern Russia, there is a tendency toward a decrease in fat intake. This recent preference has resulted in sheep breeds with high levels of fat deposition, reared over millennia, losing their importance for the production of food products [2, 9].

Sheep (*Ovis aries*) were domesticated approximately 9000-11000 years ago in the "Fertile Crescent" region in the territory of modern Iran [10]. The fat-tailed phenotype appeared much later than the thin tail phenotype.



Phylogenetic tree of Russian sheep breeds (*Ovis aries*) according to the type of wool and the type of tail. The photographs used are taken from the directory of breeds and reflect the types of livestock bred in the Russian Federation [6]. OAM — *Ovis ammon* (argali), a group that was used to root the tree (outgroup).

First, the Asiatic mouflon (*Ovis orientalis*), the presumed ancestor of modern domestic sheep [11-13], has a short, thin tail («wild» phenotype). Thus, it has been hypothesized that the first domesticated sheep were also of the short- and thin-tailed type, and breeding for fat storage in the tail or rump began several millennia after domestication [14]. Moreover, the first archeological evidence indicat-

ing the presence of fat-tailed sheep was found in the form of depictions on a stone bowl from Ur (Mesopotamia) dating to the Uruk III period of 3000 BCE [14, 15].

The formation of a fat tail as a valuable source of energy, an analog of the hump in camels and zebu cattle [9], occurred as a result of adaptation mechanisms in response to harsh natural factors: drought, severe winters, and lack of food and/or water [16].

Hardy and unpretentious sheep with fat tails and fat rumps were indispensable companions of nomadic tribes during long migrations in Eurasia and Africa [17, 18]. In terms of phylogeny (Fig.), the type of tail is the second differentiating factor, as confirmed by the results of genome studies of 25 Russian sheep breeds [19].

The advent of new technologies, including genomic editing, has created the possibility for directed and pointwise changes to the sheep genome [20-22]. Knocking out genes associated with the fat tail might be an effective strategy to eliminate the undesirable phenotype while maintaining other valuable traits of the fat-tailed breeds, such as their adaptive qualities, disease resistance, body size, and meat quality. In this regard, it is important to identify causative mutations that determine the processes of fat deposition in the tail region of sheep.

In this review, we summarize and examine the results of studies on the genetic mechanisms critical for the fat tail phenotype in sheep breeds from different parts of the world and identified candidate genes involved in the phenotype acquisition. A detailed analysis of the applied methodological and bioinformatics approaches for studying the genetics underlying the processes of fat deposition in the tails of the sheep was performed.

Scanning for signatures of selection. Domestication and long-term selection based on economically useful traits (quantity and quality of wool, meat and dairy production, and quality of sheepskins), as well as animal adaptation to new breeding conditions (climate, feed resources, and keeping systems), have significantly shaped the genomes of modern sheep breeds, including the so-called "signatures" of selection [23]. The search for genome regions under selection pressure is one of the most popular approaches for identifying candidate genes and for mapping quantitative trait loci (QTLs). This approach offers a tool for studying the evolutionary history of the populations and analyzing adaptive mutations [23] and also has important and valuable applications.

Therefore, over the past decade, signatures of selection were found in genome regions containing candidate genes that are likely associated with skin pigmentation [24-26], muscle building [27], milk production [28], reproductive traits [25, 29], wool quality [30], parasite resistance [31], and the formation of horned or hornless phenotypes [25, 29] in sheep.

Bioinformatics methods based on differences in allele frequencies (calculated Fst values) [32, 33] or on differences in haplotype frequencies between populations (the hapFLK method) [34] are used to search for selective sweeps.

The first attempts to search for candidate genes associated with fat deposition in sheep tails were made upon the advent of the OvineSNP50K BeadChip DNA assay with medium genome coverage (~ 50 K SNPs). Using this genotyping array, the International Sheep Genomics Consortium (ISGC), within the framework of the Ovine HapMap project, genotyped 2819 sheep from 74 breeds and provided access to the generated SNP profiles [25].

In 2012, M.H. Moradi et al. [9] performed a comparative screening of genome-wide genotyping data on sheep with thin and fat tails from local Iranian breeds and sheep included in the Ovine HapMap project. The research resulted in the identification of selection signatures in three genomic regions on chromosomes five, seven and X. It was reported that a high degree of homozygosity in the re-

gions of chromosomes 5 and X promotes the formation of a fat tail, and a high degree of homozygosity on chromosome 7 leads to the development of a thin tail. B. Moioli et al. studied groups including thin-tailed Italian sheep and only two European fat-tailed breeds (Laticauda and Cypriot fat-tailed) [35]. They found *BMP2* and *VRTN* and suggested that these genes are likely the most critical for the regulation of fat deposition in the tail region of sheep. Specifically, bone morphogenetic protein 2 (*BMP2*) plays an important role in the development of bones and cartilage, and vertin (*VRTN*) is crucial for variations in the number of vertebrae [36]. The *BMP2* gene was reported to be under selection pressure in local Egyptian [37] and Chinese fat-tailed sheep breeds [38].

Using an OvineSNP50K Beadchip assay, C. Wei et al. [4] proposed the *PDGFD* gene as a possible candidate involved in the differentiation of preadipocytes with high expression in adipose tissues. Recent studies have confirmed the role of the *BMP2, VRTN*, and *PDGFD* genes in the formation of the fat tail, as well as in adaptation to desert climates [39, 40]. Studying local Chinese fat-tailed sheep breeds, Z. Yuan et al. [41] found 40 potential candidate genes, the most significant of which were *HOXA11, BMP2, PPP1CC, SP3, SP9, WDR92, PROKR1*, and *ETAA1*. It should be noted that the *PROKR1* and *ETAA1* genes are involved in controlling obesity in humans [42, 43] and are likely associated with the formation of fat tails in sheep.

Genes from the *homeobox* family play important roles in the development and morphology of the skeleton, sacrum, and tail [44]. It is assumed that the *HOXA11-13* genes, regulating the number of coccygeal vertebrae, are likely more critical to the length of the tail than to the deposition of fat around the tail. Interestingly, the *HOXA11* gene was previously identified, but it was not assigned to candidates associated with the length or size of the tail [26].

A study using a high-density DNA chip, Ovine Infinium® HD SNP BeadChip assay (~ 600 K SNP), showed that the genes of the *homeobox* family were under pressure of selection in Russian fat-tailed sheep breeds. Specifically, the *HOXC* gene group on chromosome 3 in the Lezgin, Edilbaev and Karakul breeds and the *HOXA* gene group on chromosome 4 in the Karachaev and Buubei breeds were identified [45].

Using an OvineSNP50K Beadchip assay to address the genetic state of Ethiopian and Libyan local fat-tailed sheep, A. Ahbara et al. [46] found that the *ALX4, HOXB13,* and *BMP4* genes were associated with the growth and development of the limbs and skeleton and with tail formation. Further whole-genome next-generation sequencing with deep coverage revealed a strong selection signal in the representatives of these breeds in the region of the *HOXB13* gene, which confirmed the influence of it on the formation of tail types in sheep [47].

To identify candidate genes important to the short fat-tail phenotype, D. Zhi et al. [48] sequenced the whole genome of a local Chinese sheep breed Hulunbuir. Despite the ambiguous results, it was shown that the c.G334T mutation in the *T* gene, which regulates vertebra development, affects the formation of a short, fat tail in sheep, a finding partially confirmed by previous studies [49].

In addition, studies on the adaptability of fat-tailed sheep breeds to the arid climatic conditions of Egypt revealed 172 potential candidate genes that were involved in some way in the physiological mechanisms of adaptation and the regulation of the morphology of the body and its parts, including the fat tail [37, 50].

Genome-wide association study (GWAS). The genome-wide association study is a powerful bioinformatics tool for identifying genomic variations associated with quantitative traits in livestock species [51], including sheep [52, 53]. In contrast to searching for selective sweeps, to conduct a GWAS, a database on phenotype variants must be available for the trait of interest.

Combining the body measurements and genotyping data obtained using a high-density DNA chip, S. Xu et al. [54] revealed several SNPs associated with the development of a fat tail, and they were localized in the genes critical for lipid metabolism (*CREB1, STEAP4, CTBP1* and *RIP140*).

Nevertheless, no genes previously proposed as functional candidates were identified [35, 41]. It has also been suggested that the genome region between 88 and 89 Mb on the X chromosome contains a number of significant SNPs, presumably indicating that this region is potentially associated with the formation of a fat tail in sheep [54].

Copy number variation (CNV). Analysis of copy number variation is a bioinformatics approach for detecting candidate genes and identifying QTLs, as well as for studying the evolutionary mechanisms in domesticated animals and their adaptability to various environmental conditions [55]. The CNV phenomenon is based on some genome regions ranging in size from one thousand to millions of base pairs being present in several copies, the number of which varies among individuals within the population [55]. Copy number variation is an important source of genetic variation in an individual, since CNVs can alter gene expression and, accordingly, cause an unexpected phenotype due to the deletion or duplication of genes in regions of variation [56-58].

Copy number variation in the sheep genome was studied for the first time in 2011. Only 135 CNV regions were found, likely due to the unsuitability of the applied hybridization method based on cross-amplification with the cattle genome [59].

In 2016, approximately 3488 autosomal CNV regions were revealed in sheep using the specifically developed Roche NimbleGen 2.1M CGH platform (Roche NimbleGen, Inc., USA) and new CNV validation methods [60]. In addition, attempts were made to search for functional genes overlapping in the CNV regions using a medium density DNA chip [61, 62].

Using a high-density DNA chip, Zhu C. et al. [63] revealed candidate genes that fully overlap in the CNV regions and are associated with fat deposition in the tails of local Chinese sheep (the Han fat-tailed, Altay and Tibetan breeds), including the genes *PPARA, RXRA, KLF11, ADD1, FASN, PPP1CA* and *PDGFA*. Further studies provide evidence that the listed genes also overlap in the CNV region in another local Chinese breed, Tan sheep [64].

Transcriptome analysis based on NGS. The development of next-generation sequencing (NGS) methods has led to the creation of RNA-seq technology, which has taken gene expression studies to a new, high level [65]. The popularity of the RNA-seq approach is due to a number of advantages, including the unsurpassed resolution, the lack of need for preliminary knowledge of the sequence under investigation, and the ability to reanalyze the data obtained using RNA-seq, as in the case when a more relevant genome assembly becomes available [65-67].

The RNA-seq method allowed the identification of the *NELL1* and *FMO3* genes, which are likely involved in the regulation of fat metabolism in adipose tissues [68]. Excessive expression of the *NELL1* gene may be a key factor in reducing the fat deposition in the tail region [68].

The extension of studies to local Chinese sheep breeds [69, 70] revealed candidate genes that play significant roles in increased fat deposition in the tail region: *SP9* and genes of the *homeobox* family, *HOXC11, HOXC12,* and *HOXC13* [69], and *CREB1, WDR92* and *ETAA1* [70]. In addition, according to L. Ma et al. [71], the *FMO2, PLIN2, PLIN3, LEPR, PENK, ELOVL3, ELOVL5, PDK4*, and *SLC22A4* genes play key roles in fat deposition, adipogenesis, and the biosynthesis of fatty acids.

The transcriptome analysis of Chinese breeds was continued by B. Li et al. [72], who investigated the genetic regulation of lipid metabolism in fat-tailed sheep. It was established that *FABP4, ADIPOQ, FABP5* and *CD36* are the most highly transcribed genes associated with the deposition of fat in the sheep body.

The role of the *FABP4* and *FABP5* genes in the accumulation of fat in cattle [73] and in influencing meat tenderness in sheep [74] is well known. The *CD36* and *ADIPOQ* genes are transporters and regulators of fatty acids [75-77]. B. Li et al. [72] noted that the *FHC*, *FHC-pseudogene*, and *ZC3H10* genes may also be involved in the regulation of lipid metabolism in sheep [72]. The involvement of the *ZNF395* gene in adipogenesis processes has also been suggested [78].

The role of the *FABP4* gene in the processes of fat deposition in the tail region in some sheep breeds has been discussed previously, but conflicting results have been obtained. For example, M.R. Bakhtiarizadeh et al. [79], studying the expression of candidate genes, including *FABP4, FASN, SCD*, and *LPL*, found significantly higher expression of the *FABP4* gene in the fat tail compared with their expression in visceral adipose tissues ($p < 0.05$). On the other hand, X. Ruixia et al. [80], noting the high levels of expression of the *FABP4* gene in Altay, a fat-rumped breed, did not find a significant difference with *FABP4* gene expression in the control group, which consisted of sheep with thin tails. Nevertheless, any conclusion on the role of the *FABP4* gene in the formation of the fat tail and/or fat rump is premature, since the listed differences in gene expression can be breed-specific.

There is an assumption that long noncoding RNAs (lncRNAs) might be involved in the regulation of the expression of genes associated with the deposition of fat in the tails of sheep [81]. A high correlation between the expression of Lpin2 and Lpin3 mRNA and the size of fat tails was shown [82].

In addition, a difference in the expression of the *CPT1* [83] and *OXCT1* [84] genes was found in fat-tailed sheep compared with thin-tailed sheep; therefore, these genes might be considered likely candidates.

Information on the potential candidate genes identified to date is summarized in the table.

Candidate genes involved in the acquisition of the fat tail phenotype in sheep (*Ovis aries*) and methods for their identification

Gene	Chromosome	Method	Function	Reference
ADIPOQ (adiponectin)	1	RNA-seq	Oxidation of fatty acids and glucose	[72]
LEPR (leptin receptor)	1	RNA-seq	Fat deposition, adipogenesis	[71]
RIP140 (NRIP1) (nuclear receptor-interacting protein 1)	1	GWAS	Regulation of lipid and glucose metabolism	[54]
CREB1 (cAMP responsive element binding protein 1)	2	RNA-seq GWAS	Lipid metabolism, glucose homeostasis and adipocyte differentiation	[54, 70]
LPL (lipoprotein lipase)	2	RNA-seq	The release of fatty acids and glycerol through triglyceride hydrolysis	[79]
PLIN2 (perilipin 2)	2	RNA-seq	Fat deposition	[71]
SP3 (Sp3 transcription factor)	2	SPS	Inhibition of adipocyte differentiation	[41]
SP9 (Sp9 transcription factor)	2	SPS, RNA-seq	Fat deposition by adherence of mesenchymal cells to adipocytes	[41, 69]
ZNF395 (zinc finger protein 395)	2	RNA-seq	Differentiation of preadipocytes, determination of the line of progenitor cells of the mesenchyme	[78]
SLC22A4 (SLC22A family member)	3	RNA-seq	Energy metabolism, fat accumulation	[71]
CPT1 (carnitine palmitoyltransferase 1)	3	RNA-seq	Involved in the metabolism of fatty acids in the liver	[83]
ETAA1 (Ewing tumor-associated antigen 1)	3	SPS, RNA-seq	Distribution and deposition of fat in the body	[41, 70]
HOXC11 (homeobox C11-13)	3	RNA-seq, SPS	Knockout leads to vertebra transformation	[45, 69]
KLF11 (Krüppel-like factor 11)	3	CNV	Brown fat transcription factor	[64]
PPARA (peroxisome proliferator-activated receptor-α)	3	CNV	Coactivator of fatty acid metabolism	[64]
PROKR1 (prokineticin receptor 1)	3	SPS	Suppression of proliferation and differentiation of preadipocytes	[41]

Table continued

RXRA (retinoic X receptor A)	3	CNV	Lipid homeostasis	[64]
WDR92 (WD repeat domain 92)	3	SPS, RNA-seq	Interaction with phospholipids	[41, 70]
ZC3H10 (zinc finger CCCH-type containing 10)	3	RNA-seq	Adipocyte homeostasis; located in QTL associated with internal fat	[72]
HOXA11 (homeobox A11)	4	SPS	Regulation of variation in the number of coccygeal vertebrae	[26, 41, 45]
PDK4 (pyruvate dehydrogenase kinase 4)	4	RNA-seq	Fat accumulation, adipogenesis	[71]
STEAP4 (STEAP4 metalloreductase)	4	GWAS	Encodes metalloreductase involved in adipocyte metabolism in adipose tissue	[54]
PLIN3 (perilipin 3)	5	RNA-seq	Fat accumulation	[71]
ADD1 (adipocyte determination and differentiation factor 1)	6	CNV	Differentiation of adipocytes and cholesterol homeostasis	[64]
CTBP1 (C-terminal-binding protein 1)	6	GWAS	Oxidation of fatty acids; inhibition leads to fatty liver	[54]
BMP4 (bone morphogenetic protein 4)	7	SPS	Growth and development of limbs, skeleton and tail formation	[46]
VRTN (vertnin, vertebrae development associated)	7	SPS	Change in the number of vertebrae	[35, 39, 40]
T(TBXT) (T-box transcription factor T, T/Brachyury)	8	SPS	Development of vertebrae, the formation of a short, fat tail in sheep	[48, 49]
FABP4 (fatty acid-binding protein 4)	9	RNA-seq	Transportation of fatty acids to locations of accumulation or production of energy; high expression increases adipocyte differentiation time	[72, 79, 80]
FABP5 (fatty acid-binding protein 5)	9	RNA-seq	Compensation for FABP4 loss in adipocytes	[72]
PENK (proenkephalin)	9	RNA-seq	Fat accumulation	[71]
FASN (fatty acid synthase)	11	CNV	De novo fatty acid synthesis, fat accumulation and fatty acid anabolism	[64]
HOXB13 (homeobox B13)	11	SPS	Growth and development of limbs, skeleton and tail formation	4[6, 47]
FMO2 (flavin-containing dimethylaniline monoxygenase 2)	12	RNA-seq	Fat accumulation, adipogenesis and fatty acid biosynthesis	[71]
BMP2 (bone morphogenetic protein 2)	13	SPS	Development of bones and cartilage	[35, 37-41]
Lpin3 (lipin 3)	13	RNA-seq	Lipid metabolism	[82]
ALX4 (ALX homeobox 4)	15	SPS	Growth and development of limbs, skeleton and tail formation	[46]
PDGFD (platelet-derived growth factor D)	15	SPS	Inhibition of differentiation of preadipocytes	[4, 39, 40]
OXCT01 (3-oxoacid CoA-transferase 1)	16	RNA-seq	Metabolism of ketone bodies; knockout leads to lipid accumulation in adipocytes	[84]
PPP1CC (protein phosphatase 1 catalytic subunit gamma)	17	SPS	Dephosphorylation and inactivation of glycogen synthase in skeletal muscle	[41]
ELOVL5 (fatty acid elongase 5)	20	RNA-seq	Elongation of polyunsaturated long-chain fatty acids	[71]
FHC (ferritin heavy chain)	21	RNA-seq	Regulation of fat cell activity	[72]
FMO3 (flavin-containing monooxygenase 3)	21	RNA-seq	Inhibition of fatty acid oxidation	[68]
NELL1 (NEL-like 1 neural EGFL-like 1, a protein strongly expressed in neural tissue encoding an epidermal growth factor-like domain)	21	RNA-seq	Enhancement of osteogenic differentiation and weakens the differentiation of adipose tissue	[68]
PPP1CA (phosphoprotein phosphatase 1 catalytic subunit)	21	CNV	Conversion of phosphorylase A to phosphorylase B	[64]
ELOVL3 (ELOVL fatty acid elongase 3)	22	RNA-seq	Energy metabolism, lengthening saturated and monounsaturated fatty acid chains	[71]
Lpin2 (lipin 2)	23	RNA-seq	Involvement in lipid metabolism	[82]
PDGFA (platelet-derived growth factor alpha)	24	CNV	Differentiation of preadipocytes	[64]

N o t e . RNA-seq — transcriptome analysis of gene expression based on next-generation sequencing (NGS), CNV — copy number variation, SPS — scan for signatures of selection, selective sweeps, GWAS — genome-wide association study

To search for candidate genes associated with the formation of fat tails in Russian sheep breeds, at the Ernst Federal Science Center for Animal Husbandry, a resource sheep population was obtained from crossing the long-fat-tailed Karachaev and short-thin-tailed Romanov sheep breeds. The sizes of the tails of the

F_2 hybrids and backcrosses will be measured 6, 42, 90 and 180 days after birth. The animals of the resource population will be genotyped using high-density DNA chip and analyzed using GWAS. The use of resource populations for QTL mapping has several advantages over the use of random populations: in particular, a decrease in the false discovery rates (FDR) and an increase in the accuracy of mapping [85]. In this regard, the identified candidate genes associated with fat deposition in the tails in the Russian breeds might be used as possible targets for editing the genome of fat-tailed sheep to increase the production of lean mutton.

Thus, we summarized and analyzed the results of the investigations of the world scientific community on the identification of candidate genes associated with increased fat deposition in the tail region of sheep. We reviewed the most popular methods for identifying potential candidate genes, including scanning for selection signatures, genome-wide associative studies, copy number variation, and gene expression studies based on transcriptome analysis. The advantages and limitations of the relevant methodological approaches were analyzed. Therefore, genome-wide association studies are high-resolution and effective methods of QTL mapping, but their implementation requires the availability of a database of phenotype variants of the economically relevant trait under investigation. To search for selection signatures and to address copy number variation, information on the phenotypes is optional, but the results obtained using both approaches require validation by quantitative PCR amplification or sequencing of the identified genome regions. Transcriptome analysis is a high-resolution method, but the collection of the organ and tissue specimens must be considered based on strict time and temperature conditions. The most significant candidate genes associated with the deposition of fat in sheep tails and identified in more than one study, including *BMP2* and *VRTN*; *PDGFD*; genes of the *homeobox* family; *SP9*; *CREB1*; *PPARA*, *RXRA*, *KLF11*, *ADD1*, *FASN*, *PPP1CA* and *PDGFA*, are presented. Despite a significant number of studies aimed at identifying the genetic mechanisms underlying the fat tail phenotype in sheep, the only known fact is that more than one gene is involved in the formation of a fat tail. As a method for searching for candidate genes involved in the acquisition fat tails in Russian sheep breeds, a genome-wide association study on sheep from a resource sheep population, obtained by crossing long-fat-tailed Karachaev sheep with short-thin-tailed Romanov sheep, has been proposed.

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