AGRICULTURAL BIOLOGY,
2021, V. 56, Iss. 6, pp. 1049-1062
[SEL'SKOKHOZYAISTVENNAYA BIOLOGIYA]

ISSN 2412-0324 (English ed. Online)
ISSN 0131-6397 (Russian ed. Print)
ISSN 2313-4836 (Russian ed. Online)

UDC 636.32/.38:636.082:577.21

doi: 10.15389/agrobiology.2021.6.1049eng
doi: 10.15389/agrobiology.2021.6.1049rus

INTRAMUSCULAR FATTY ACID COMPOSITION IN SHEEP: PHENOTYPIC VARIABILITY, HERITABILITY, AND CANDIDATE GENES

(review)

S.N. KOVALCHUK ✉

Institute of Innovative Biotechnologies in Animal Husbandry — the Branch of Ernst Federal Research Center for Animal Husbandry, 12/4, ul. Kostyakova, Moscow, 127422 Russia, e-mail s.n.kovalchuk@mail.ru (✉ corresponding author)
ORCID:
Kovalchuk S.N. orcid.org/0000-0002-5029-0750
The author declares no conflict of interests
Acknowledgements:
Funded by the Ministry of Science and Higher Education of the Russian Federation (theme No. AAAA-A19-119051590015-1)
Received October 2, 2021

Abstract

Sheep husbandry contributes significantly to global food production. Improving the biochemical parameters of meat is one of the urgent goals of sheep breeding programs due to the changed customers' requirements for food quality, in particular its dietary properties. The fatty acid composition is one of the important indicators of meat quality. High concentrations of saturated fatty acids in the human diet are known to increase plasma cholesterol concentrations which increases the risk of developing diabetes, obesity, and cardiovascular disease (A.P. Simopoulos, 2001; F.B. Hu et al., 2001). Improving the dietary properties of sheep meat by breeding animals with the increased content of unsaturated fatty acids is one of the possible measures that could reduce the incidence of these diseases. In addition, intramuscular fatty acid composition affects flavor, aroma, juiciness, and tenderness of the meat and the digestibility of fat. These reasons determine the relevance of identifying genetic markers associated with intramuscular fatty acid composition in sheep and their use in sheep breeding programs. This review analyzes data on phenotypic variability, inheritance of the intramuscu-lar fatty acid composition in sheep, and candidate genes identified due to genome-wide association studies (GWAS) with DNA microarrays technology (R. Bumgarner 2013) and high-throughput RNA sequencing method (RNA-seq) applicable in studying genetic mechanisms that are involved in the formation of animal phenotypes at the gene expression level (A. Oshlack et al., 2010; K.O. Mutz et al., 2013; R. Stark et al., 2019). Research results demonstrate that the quantitative indicators of the intramuscular fatty acid composition in different breeds of sheep and the degree of heritability of this trait vary widely which indicates the possibility of changing the profiles of the fatty acid composition of mutton through the use of genetic methods in sheep breeding programs (E. Karamichou et al., 2006; H.D. Daetwyler et al., 2012; S.I. Mortimer et al., 2014; S. Bolormaa et al., 2016; G.A. Rovadoscki et al., 2017**).** Summarizing GWAS и RNA-seq results, the most significant candidate genes associated with the fatty acid composition of sheep meat are i) *acot11*, *baat*, *pnpla3*, *lclat1*, *isyna1*, *elovl6*, *agpat9*, *me1, acaca*, *dgat2*, *plcxd3*, *fads2*, *scd*, *cpt1a*, *pisd*, *lipg*, *b4galt6*, *acsm1*, *acsl1*, *aacs*, and *fasn* which encode the enzymes of fat and fatty acids metabolism; ii) the genes encoding fatty acid transporters FABP3, FABP4, FABP5, SLC27A6, APOL6, and COPB2; iii) *mlxipl*, *ppard*, *wnt11, foxo3*, *tnfaip8*, *npas2*, *fndc5*, *adipoq*, *adipor2*, *trhde*, *cidec*, *ccdc88c*, *tysnd1* and *sgk2* genes which encode the transcription factors and effector proteins, regulating energy and fat metabolism (X. Miao et al., 2015; S. Bolormaa et al., 2016; L. Sun et al., 2016; G.A. Rovadoscki et al., 2017; R. Arora et al., 2019). These data allow a deeper understanding of the genetic mechanisms underlying the phenotypic variability of intramuscular fatty acid composition in sheep, which is a necessary background for successful selection strategies in sheep husbandry.

Keywords: sheep, fatty acids, genetic markers, GWAS, RNA-seq, SNP

Sheep farming significantly contributes to world food production. Currently, gene pool of sheep bred in more than 150 countries comprises more than 2300 breeds. In the Russian Federation, 46 breeds of sheep are raised of which 15

are fine-wool sheep, the share of which in 2020 was 53.6% of the total livestock at agricultural enterprises, 14 are semi-fine-wool sheep (5.0%), 2 are semi-coarse-wool sheep (1.4%), 15 are coarse-haired sheep (34.3%) [1]. The general trend of modern world sheep breeding is the reduction in the number of woolly sheep. From 2000 to 2020 in Russia, the share of fine-wool sheep decreased by 26.9%, of semi-fine-wool sheep 2.6-fold, while the share of coarse-wool breeds bred for meat production increased 6.4-fold [1]. The main reason for the reduction in the need for sheep wool is the rapid growth in the production of synthetic fibers, the quality of which, in many respects, is close to natural at a much lower cost. Currently, the share of meat products in the gross income from the sale of all products obtained from sheep approximates to 90% [2, 3]. The intensification of sheep breeding and the growing demand for mutton in many countries is accompanied by the emergence of new, more productive sheep breeds. Selection is aimed at creating sheep breeds with a combined high wool and meat productivity [3].

One of the ways to improve sheep breeds is to improve the biochemical parameters of meat, which is due to the changed requirements for the quality of food products, in particular, for their dietary properties. The average content of saturated fatty acids in mutton is 1.464 g/100 g of meat, which is higher than in beef and pork (respectively 1.149 and 0.400 g/100 g meat) [4]. Lamb significantly exceeds beef and pork (more than 1.5-fold and 10-fold) in the content of polyunsaturated ω-3 and ω-6 fatty acids [4], which are not synthesized in the human body [5], but are involved in the synthesis of eicosanoids, cell signaling, regulation of enzyme and neurotransmitter activity, neuronal migration, and other vital processes [6, 7]. For an adult, the physiological need for ω-6 fatty acids is 8-10 g per day, for ω-3 fatty acids 0.8-1.6 g per day, with the optimal ratio of ω-6 to ω-3 fatty acids within 5:1-10:1 [8].

A high content of saturated fatty acids in the human diet is known to increase the blood cholesterol concentration and, as a result, increase the risk of cardiovascular diseases, diabetes and obesity [9, 10]. In addition, the fatty acid composition of meat affects its consumer properties, e.g., flavor, odor, juiciness, tenderness and digestibility. The more unsaturated fatty acids in the composition of the fat, the lower its pour point and the higher the digestibility. Therefore, it is important to identify and use in breeding genetic markers associated with the fatty acid composition of sheep meat.

The emergence in recent decades of high-throughput DNA sequencing (next generation sequencing, NGS) technologies [11, 12] and their widespread use has made it possible to establish the nucleotide sequences of the genomes of most agricultural animal species, including sheep [13, 14]. In turn, this contributed to the development of DNA chip technology [15] for genome-wide association analysis to identify candidate genes and genomic variations (single nucleotide polymorphisms, SNPs) associated with economically important traits in crops and domestic animals [16-18].

The later developed RNA sequencing technology (RNA-seq) makes it possible to study the genetic mechanisms of phenotype formation based on a comparative analysis of gene expression profiles. [19-22]. The integrated use of these approaches contributes to the understanding of the genetic mechanisms underlying the variability of economically useful traits of farm animals, which serves as the necessary scientific basis for the development of successful breeding programs in animal husbandry [23, 24].

This review analyzes and summarizes the results of studies of the phenotypic variability and heritability of fatty acid composition of sheep muscle tissue, as well as data on candidate genes identified using genome-wide association search and high-throughput RNA sequencing.

The heritability of the content of fatty acids in the muscle tissue of sheep. The quality of lamb, including its fatty acid composition, depends on the breed [25-28], sex and age of the animals [29-31], as well as on the diet [32-34]. Quantitative indicators of the fatty acid composition of sheep meat of different breeds vary widely and differ in breeds of both the same and different directions of productivity (Table 1).

1. Lamb fatty acid composition in various breeds of sheep (*Ovis aries*) (*M*±SEM)

Fatty acids	Breed					
	Edilbay [29]	Romanian [31]	Prekos [27]	Karachai [30]	Kubashev [28]	Tsigai [28]
	meat-fat	meat-wool				wool-met
Saturated:						
myristic, $C_{14:0}$	8.11±0.10	2,51±0,45	5,00±0,25	3,50±0,11	2,42±0,19	4,98±0,12
pentadecanoic, $C_{15:0}$		0,68±0,51		0,99±0,03	0,76±0,06	
palmitic, $C_{16:0}$	24.15±0.14	22,31±1,53	25,00±0,08	25,32±1,19	22,29±0,29	25,02±0,07
stearic, $C_{18:0}$	21.98±0.23	24,71±0,63	25,00±0,10	22,51±0,96	46,76±0,34	25,02±0,11
Monounsaturated:						
palmitoleic, $C_{16:1}$	1.38±0.11	2.54±0,13		2,54±0,08	4,33±0,20	
heptadecenoic, $C_{17:1}$	0.60±0.09	0,54±0,12			2,01±0,14	
oleic, $C_{18:1}$	32.8±0.22	41,09±1,68	39,00±0,18	39,44±1,16	15,8±0,24	38,98±0,23
Polyunsaturated:						
linoleic, $C_{18:2\omega6}$	5.32±0.14	2,54±1,09	4,00±0,15	2,24±0,09		3,99±0,09
linolenic, $C_{18:3\omega3}$	0.99±0.07	0,93±0,08	0,50±0,02	0,86±0,02	0,73±0,09	0,55±0,02
arachidonic, $C_{20:4\omega6}$	0.27±0.03		1,50±0,04	0,090±0,004		1,46±0,05

N o t e. Gaps mean no data.

2. Reported heritability (h^2) **of fatty acid content in muscle tissue of various breeds of sheep (*Ovis aries*)** (*M*±SEM)

Fatty acids	h^2			
	[36]	[37]	[38]	[39]
Saturated:				
myristic, $C_{14:0}$	0.19±0.14		0,15	0,44±0,045
palmitic, $C_{16:0}$	0.29±0.17		0,11	0,25±0,033
stearic, $C_{18:0}$	0.24±0.15		0,19	0,30±0,037
Monounsaturated:				
palmitoleic, $C_{16:1}$	0.31±0.18			0,30±0,035
oleic, $C_{18:1}$	0.27±0.17			0,28±0,035
Polyunsaturated:				
arachidonic, $C_{20:4\omega6}$	0.60±0.17	0,15±0,04	0,16	
linoleic, $C_{18:2\omega6}$	0.10±0.09	0,22±0,04	0,15	0,27±0,034
conjugated linoleic, CLA_{c9t11}	0.48±0.06			0,34±0,045
α-линоленовая кислота, $C_{18:\omega3}$	0.30±0.02			0,46±0,045
Total content of saturated fatty acids	0.90±0.16			0,32±0,039
Total content of monounsaturated fatty acids	0.73±0.18			0,31±0,038
Total content of polyunsaturated fatty acids	0.40±0.16			0,28±0,034
Total content of ω-3 fatty acids				0,37±0,045
Total content of ω-6 fatty acids				0,27±0,034
Polyunsaturated/saturated fatty acids				0,28±0,034
ω6/ω3 ж fatty acids				0,33±0,042

N o t e. Data on Texel, Border Leicester, Polled Dorset, Suffolk, East Friesian, Merino sheep [36], Merino sheep [37], Merino, Poll Dorset, Border Leicester, Suffolk, Texel, Corriedale, Coopworth sheep and crosses [38], Santa Inês [39] are submitted. Gaps mean no data.

For the first time, the degree of heritability of the content of fatty acids in the muscle tissue of sheep was estimated by Karamichou et al. [35] in 2006 based on a study of two lines of Scottish Blackface sheep that differed in the fatty acid composition of the *longissimus dorsi* muscle. It was shown that the total content of saturated and monounsaturated fatty acids are highly inherited traits (h^2 heritability coefficients of 0.90 and 0.73, respectively); the total content of polyunsaturated fatty acids is a moderately inherited trait ($h^2 = 0.40$) (Table 2).

Later, similar studies were carried out for more than a dozen breeds and crosses of sheep [36-39]. Daetwyler et al. [36] conducted a genomic assessment of the breeding value of sheep based on the analysis of the databases of the Cooperative

Research Center for Sheep Industry Innovation [40] and SheepGENOMICS [41], including 14039 breeds Texel, Border Leicester, Polled Dorset, Suffolk, East Friesian and Merino. It was revealed that the intramuscular fat content refers to moderately inherited traits ($h^2 = 0.49$), while this indicator for eicosapentaenoic and docosapentaenoic polyunsaturated fatty acids was significantly lower and amounted to 0.26 and 0.24, respectively [36], which agrees with the data of Mortimer et al. [37]. Bolormaa et al. [38] studied 10613 Merino, Poll Dorset, Border Leicester, Suffolk, Texel, Corriedale, Coopworth and cross breed sheep and found low heritability coefficients ($h^2 = 0.15$-0.19) for both polyunsaturated arachidonic, linoleic, and for saturated $C_{14:0}$, $C_{16:0}$ and $C_{18:0}$ fatty acids (see Table 2). The results of a study of 216 sheep of the Santa Inês breed revealed a moderate heritability of all fatty acids studied by the authors, among which the highest values of the coefficient of heritability were in α-linolenic and myristic acids [39].

Thus, the heritability coefficients of the content of fatty acids in the muscle tissue of sheep varied over a wide range, which indicates a significant genetic variability of the estimated traits in different breeds and, therefore, the possibility of changing the profiles of the fatty acid composition of meat in sheep through the use of genetic methods in breeding.

Quantitative trait loci and candidate genes associated with fatty acid content. More than 20 QTLs (quantitative trait loci) associated with fatty acid content in sheep muscle tissue have been annotated in the SheepQTLdb database [42, 43].

For the first time, loci of quantitative traits of the fatty acid composition of sheep meat were identified by Karamichou et al. [35] in 2006. A total of 21 QTLs were found on chromosomes 1, 2, 3, 5, 14, 18, 2 and 21, most of which were associated with the content of certain fatty acids, and not with their total number [35]. Rovadoscki et al. [39] performed genome-wide association studies based on the genotyping of 216 Santa Inês sheep using the OvineSNP50 BeadChip DNA chip (Illumina, Inc., USA), as a result of which 27 QTLs were detected on chromosomes 1, 2, 3, 5, 8, 12, 14, 15, 16, 17 and 18 and 23 potential candidate genes were found, including *dgat2*, *trhde*, *tph2*, *me1*, *parp14*, and *mrps30* associated with fatty acid content in sheep muscle tissue (Table 3). Thus, QTLs of the total content of saturated fatty acids were found on chromosomes 3, 14, and 15 and included the *tph2*, *trhde*, *dgat2*, *wnt11*, and *npas2* genes. The *tph2* gene encodes the enzyme tryptophan hydroxylase 2 (TPH2), which is associated with the serotonergic system and is involved in various physiological processes, including lipid metabolism in adipose tissue [44, 45]. The enzyme pyroglutamyl peptidase II (TRHDE, product of the *trhde* gene) inactivates thyrotropin-releasing hormone, which regulates energy metabolism [46]. The association of the *trhde* gene with the content of visceral fat in Merino sheep was previously shown [47]. The neuronal PAS domain-containing protein 2 (NPAS2) plays an important role in the PPAR signaling pathway that regulates lipid metabolism with the participation of the PPARα receptor (peroxisome proliferator-activated receptor α), which controls fatty acid beta-oxidation [48, 49]. The enzyme diacylglycerol O-acyltransferase 2 (DGAT2) plays a key role in triglyceride biosynthesis [50, 51]. The *wnt11* gene is associated with the Wnt signaling pathway which has an inhibitory effect on adipogenesis [52-55].

Four QTLs were found on chromosomes 1, 3, and 15, associated with the total amount of monounsaturated fatty acids (see Table 3) and containing the *copb2* and *dgat2* genes. The COPB2 protein (coatomer subunit beta 2) plays an important role in the metabolic pathways associated with the intracellular transport of cholesterol and sphingolipids from the endoplasmic reticulum to the Golgi apparatus [56]. The QTL for oleic acid ($C_{18:1}$) is located on chromosome 15, overlaps

with the QTL for stearic acid ($C_{18:0}$) and includes the *dgat2* gene. For α-linolenic ($C1_{8:3\omega3}$), linoleic ($C_{18:2\omega6}$), conjugated linoleic (CLA_{c9t11}) polyunsaturated fatty acids, as well as total polyunsaturated fatty acids, 11 QTLs and 12 candidate genes were found, including *me1*, *tnfaip8*, *plcxd3*, *ccdc88c* and *cacna1c* located on eight chromosomes (see Table 3). The ME1 enzyme (malic enzyme 1) is associated with the tricarboxylic acid cycle, in which NADPH and acetyl-CoA necessary for the biosynthesis of fatty acids are synthesized [57]. The TNFAIP8 protein (tumor necrosis factor TNF-alpha-induced protein 8) is involved in maintaining immune homeostasis and regulating the expression of genes encoding lipid metabolism enzymes [58]. PLCXD3 (phosphatidylinositol-specific phospholipase C, X domain containing 3) refers to phospholipases that break down phospholipids into fatty acids and other lipophilic molecules [39)]. The *cdc88c* gene product regulates the Wnt signaling pathway that affects lipid metabolism and adipogenesis [53]. The CACNA1C protein (voltage-dependent l-type calcium channel subunit alpha-1 C), like long-chain fatty acids, is involved in the functioning of calcium channels [59, 60].

3. Candidate genes associated with fatty acid content in muscle tissue of sheep (*Ovis aries*)

Gene and the encoded protein	Chromosome	Method	Function	References
adipoq (adiponectin)	1	RNA-seq	Regulation of energy homeostasis	[66]
adipor2 (adiponectin receptor 2)	1	RNA-seq	Regulation of energy homeostasis	[66]
acot11 (acyl-CoA-thioesterase 11b)	1	RNA-seq	Lipid metabolism enzyme	[66]
copb2 (coatomer subunit beta 2)	1	GWAS	Intracellular fat transport	[39]
baat (bile acid-coenzyme A: amino acid N-acyltransferase)	2	RNA-seq	Lipid metabolism enzyme	[84]
cyp27a1 (sterol 26-hydroxylase)	2	GWAS	Breakdown of cholesterol	[38]
fabp5 (fatty acid binding protein 5)	2	RNA-seq	Transport of long-chain fatty acids, compensation for loss of FABP4 in adipocytes	[80]
fndc5 (6fibronectin type III domain-containing protein 5)	2	RNA-seq	Regulation of adipose tissue metabolism	[66]
fabp3 (fatty acid binding protein 3)	2	RNA-seq	Regulation of intramuscular fat content, adipogenesis	[66]
trhde (pyroglutamyl-peptidase II)	3	GWAS	Regulation of energy metabolism	[39]
apol6 (apolipoprotein L6)	3	GWAS	Lipid transport	[38]
cacna1c (voltage-dependent l-type calcium channel subunit alpha-1 C)	3	GWAS	Transmembrane transport of calcium ions	[39]
npas2 (neuronal PAS-containing domain protein 2)	3	GWAS	Regulation of fat metabolism with PPAR	[39]
tph2 (tryptophan hydroxylase 2)	3	GWAS	Biosynthesis of serotonin	[39]
pnpla3 (adiponutrin)	3	GWAS	Release of fatty acids and glycerol via hydrolysis of triglycerides	[38]
lclat1 (lysocardiolipin acyltransferase 1)	3	RNA-seq	Lipid metabolism enzyme catalyzing the acylation of polyglycerophospholipids	[84]
tnfaip8 (tumor necrosis factor (TNF)-alpha-induced protein 8)	5	GWAS	Regulation of the expression of enzymes involved in the metabolism of lipids and fatty acids	[39]
slc27a6 (solute carrier family 27 member 6)	5	RNA-seq	Fatty acid transport	[84]
isyna1 (inositol-3-phosphate synthase 1)	5	GWAS	Biosynthesis of phospholipids	[38]
snora70 (small nucleolar RNA, H/ACA box 70)	6	GWAS	RNA processing	[38]
elovl6 (elongation of very long chain fatty acids protein 6)	6	GWAS	Fatty acid elongation	[38, 80]
agpat9 (1-acylglycerol-3-phosphate O-acyltransferase 9)	6	GWAS	Biosynthesis of triglycerides	[38]
foxo3 (forkhead box protein O3)	8	GWAS	Transcription factor regulating glucose metabolism, cell cycle and apoptosis	[39]
me1 (malic enzyme 1)	8	GWAS	Biosynthesis of fatty acids	[39]
fabp4 (fatty acid binding protein 4)	9	RNA-seq	Delivery of fatty acids to mitochondria	[66]
dgkh (diacylglycerol kinase eta)	10	RNA-seq	Regulation of intracellular concentrations of diacylglycerol and phosphatidic acid	[84]

Continued Table 3

acaca (acetyl-coA carboxylase 1)	11	GWAS	Biosynthesis of fatty acids	[38]
fasn (fatty acid synthase)	11	GWAS	De novo fatty acid biosynthesis, fat deposition and fatty acid anabolism	[38]
synrg (synergin gamma)	11	GWAS	Participation in the transport of proteins through the Golgi apparatus	[38]
sgk2 (serum/glucocorticoid regulated kinase 2)	13	GWAS	Participation in the intracellular signaling pathway PI3K/AKT/mTOR, regulating glucose metabolism, cell proliferation and apoptosis	[38]
gys1 (glycogen synthase, muscle)	14-я	GWAS	Intramuscular glycogen synthesis	[38]
dgat2 (diacylglycerol O-acyltransferase 2)	15	GWAS	Biosynthesis of triglycerides	[39]
wnt11 (Wnt family member 11)	15	GWAS	Regulation of adipogenesis	[39]
plcxd3 (phosphatidylinositol-specific phospholipase C, X domain containing 3)	16	GWAS	Breakdown of phospholipids into fatty acids and other lipophilic molecules	[39]
cdh12 (кадгерин 12; cadherin 12)	16	GWAS	Intercellular adhesion protein	[39]
aacs (acetoacetyl-CoA synthetase)	17	RNA-seq	Enzyme for the biosynthesis of cholesterol and fatty acids	[66]
pisd (phosphatidylserine decarboxylase proenzyme, mitochondrial)	17	RNA-seq	Phospholipid biosynthetic enzyme	[84]
fbln5 (fibulin-5)	18	GWAS	Participation in the formation of elastic fibers	[39]
ccdc88c (coiled-coil domain-containing protein 88C)	18	GWAS	Downregulation of the Wnt signaling pathway involved in lipid metabolism	[39]
cidec (CIDE-N domain-containing protein)	19	RNA-seq	Deposition of fats in adipocytes, regulation of adipocyte apoptosis	[66]
ppard (peroxisome proliferator-activated receptor delta)	20	RNA-seq	Transcription factor regulating lipid metabolism	[66]
fads2 (fatty acid desaturase 2)	21	GWAS	Biosynthesis of unsaturated fatty acids	[38]
scd (stearoyl-CoA desaturase)	22	GWAS	Biosynthesis of unsaturated fatty acids	[38]
cpt1a (carnitine-palmitoyltransferase 1)	21	RNA-seq	Breakdown of long chain fatty acids	[84]
lipg (lipase endothelial)	23	RNA-seq	Fat metabolism	[84]
b4galt6 (beta 1,4-galactosyltransferase 6)	23	RNA-seq	Sphingolipid metabolism	[84]
mlxipl (MLX interacting protein like)	24	GWAS	Transcription factor that activates promoters of triglyceride synthesis genes	[38]
acsm1 (acyl-coenzyme A synthetase ACSM1, mitochondrial)	24	RNA-seq	Biosynthesis of fatty acids	[66]
tysnd1 (trypsin like peroxisomal matrix peptidase 1)	25	RNA-seq	Participation in the processing of proteins involved in beta-oxidation of fatty acids	[66]
acsl1 (long-chain-fatty-acid-CoA ligase 1)	26	GWAS	Fatty acid metabolism	[38]

Bolormaa et al. [38] used GWAS technology to study 10613 sheep and identified several potential candidate genes involved in the biosynthesis of fatty acids and triglycerides, the most significant of which are *fasn*, *mlxipl*, *elovl6*, *acaca*, *synrg*, *acsl1*, *isyna1*, *sgk2*, *fads2*, and *agpat9* genes. The *fasn*, *acaca*, *elovl6*, and *fads2* genes encode enzymes that are directly involved in fatty acid biosynthesis [62]. The *agpat9* gene encodes 1-acylglycerol-3-phosphate-O-acyltransferase 9 (AGPAT9), a key enzyme in triglyceride biosynthesis that catalyzes the conversion of glycerol-3-phosphate to lysophosphatidic acid during the synthesis of triglycerides [63]. The MLXIPL (MLX interacting protein like) protein activates promoters of triglyceride synthesis genes [64]. The enzymes long-chain-fatty-acid-CoA ligase 1 (ACSL1) and inositol-3-phosphate synthase 1 (ISYNA1) are involved in lipid biosynthesis and fatty acid degradation [65].

Arora et al. [66] performed a comparative analysis of the transcriptome profiles of *musculus longissimus thoracis* of Bandur sheep and local Indian sheep based on the RNA-seq method. Expression levels of the *adipoq*, *adipor2*, *fabp3*,

fabp4, *aacs*, *acsm1*, *acot11*, *cidec*, *fndc5*, *ppard*, and *tysnd1* genes associated with fatty acid metabolism were higher in Bandur sheep, distinguished by meat tenderness, high fat and oleic acid content compared to local sheep populations. The *fabp3*, *fabp4*, and *adipoq* genes encode proteins that play an important role in the regulation of lipid and glucose homeostasis in adipocytes [67, 68]. FABP3 and FABP4 belong to the family of fatty acid-binding proteins (FABPs). FABP3 is involved in the metabolism of long-chain fatty acids, transporting them to the mitochondria for oxidation, and also regulates adipogenesis [69]. FABP4 is one of the predominant proteins in the soluble fraction of adipose tissue, the function of which is to regulate lipolysis in adipocytes by activating hormone-sensitive lipase (HSL), leading to an increase in intracellular fatty acids [70, 71]. Recent studies have shown a negative correlation between *fabp4* gene transcription and the ratio of polyunsaturated to saturated fatty acids in *musculus longissimus dorsi* of Chinese Tan sheep [72]. The protein ADIPOQ (adiponectin) and its receptor ADIPOR2 (adiponectin receptor 2) are involved in maintaining energy homeostasis by regulating glucose levels and fatty acid oxidation [73, 74]. Previously, 9 sheep haplotypes for the *adipoq* gene were identified [75], and haplotypes B1 and A3 were shown to be associated with an increase in lean meat yield in New Zealand Romney sheep [76]. Peptidase TYSND1 (trypsin like peroxisomal matrix peptidase 1) is involved in the processing of proteins involved in beta-oxidation of fatty acids [77]. The *fabp4*, *adipoq*, and *fabp5* genes associated with fat deposition also turned out to be the most transcribed in the tail adipose tissue of fat-tailed sheep [78, 79].

Sun et al. [80] performed a comparative analysis of the transcriptome profiles of the *longissimus dorsi* muscle in two Chinese sheep breeds and identified 960 genes with different expression levels, including *elovl6* and *fabp5*, directly associated with the synthesis and transport of fatty acids [81, 82]. The *elovl6* gene encoding elongation of very long chain fatty acids protein 6 (ELOVL6) was also proposed by Bolormaa et al. [38] as a candidate gene associated with fatty acid content in sheep muscle tissue. It should be noted that polymorphism in the promoter region of the *elovl6* gene in pigs is associated with the content of palmitic and palmitoleic acids in muscles and fat [83].

Miao et al. [84] using transcriptome analysis of *musculus longissimus dorsi* of Dorset and Small Tail Han sheep, identified differentially expressed genes *cpt1a*, *baat*, and *slc27a6* associated with fatty acid biosynthesis and metabolism [85-87]. Expression of the *cpt1a* and *slc27a6* genes was also high in the tail adipose tissue of sheep [88].

There are data on the relationship of allelic variants of the calpastatin gene with the fatty acid composition of lipids in the muscle tissue of lambs. In sheep, two allelic variants of the *cast* gene, *N* and *M* were identified [89], and it was shown that the carriers of the *NN* genotype had more myristic (C*14:0)*, palmitic ($C_{16:0}$), stearic ($C_{18:0}$), arachidic ($C_{20:0}$), palmetic ($C_{16:1}$) and arachidonic ($C_{20:4}$) fatty acids than in lambs of the *MM* genotype [90]. SNPs C24T, G62A, G65T, and T69 were also found in the intron 5, c.197A > T and c.282G > T in the exon 6 of the *cast* gene; six corresponding genotypes are B, C, D, F, I, and J. Animals of genotype I have been shown to have a lower palmitic acid content and a ratio of ω6 to ω3 fatty acids and a higher content of palmitoleic acid compared to carriers of other genotypes [91].

Thus, at present, genome-wide association studies and sequencing of transcriptomes of sheep muscle tissue identified QTLs and a number of candidate genes associated with the content of fatty acids in muscle tissue. Of these, the genes *acot11*, *baat*, *pnpla3*, *lclat1*, *isyna1*, *elovl6*, *agpat9*, *me1*, *acaca*, *dgat2*, *plcxd3*, *fads2*, *scd*, *cpt1a*, *pisd*, *lipg*, *b4galt6*, *acsm1*, *acsl1*, *aacs* and *fasn* encode enzymes of fat and fatty acids metabolism. The genes *fabp3*, *fabp4*, *fabp5*, *slc27a6*, *apol6*

and *copb2* encode transporter proteins of fatty acids and fats. The genes *mlxipl*, *ppard*, *wnt11*, *foxo3*, *tnfaip8*, *npas2*, *fndc5*, *adipoq*, *adipor2*, *trhde*, *cidec*, *ccdc88c*, *tysnd1* and *sgk2* encode transcription factors and effector proteins that regulate energy and fat metabolism. Further research is needed to validate the identified candidate genes and their allelic variants as genetic markers of fatty acid content in sheep muscle tissue for use in breeding to improve lamb quality.

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