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SEQUENCING OF THE *NFE2L1* GENE IN SHEEP AND EVALUATION INFLUENCE OF GENE POLYMORPHISMS ON MEAT PRODUCTION

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ABSTRACT

The aim of this study was to investigate influence of the *NFE2L1* gene polymorphisms on some parameters of meat production in sheep. Polymorphisms of the *NFE2L1* gene were detected using NimbleGen sequencing technology (Roche, USA). The effect of polymorphisms identified was investigated in Manych Merino sheep breed. In coding and regulatory parts of gene 11 single nucleotide polymorphisms (SNP) were detected. These are the substitutions: c.-1092T>C, c.-703C>T, c.582C>T, c.788C>T, c.864C>T, c.*177C>G, c.*179C>T, c.*181C>A, c.*182G>T, c.*187G>T and c.*188G>T. Five of these SNP has been identified for the first time. Three of founded SNP c.788, c.-1092 and c.*188 have positive effect on vital meat production indicators in sheep. Another SNP c.864 have a negligible effect on investigated parameters. Consequently, the determination of allelic variants of the *NFE2L1* gene may be used in marker-assisted selection. In future will evaluate the influence of founded SNP on slaughter parameters of meat production.

Key words: NFE2L1, Sheep, Manych Merino, SNP, Sequence

INTRODUCTION

Methods of marker-assisted selection in meat production are most often based on an assessment of structure of the genes, which regulating growth of muscle tissue. These are *MSTN* (Clop *et al.*, 2006), *MyoD1* (Lôbo *et al.*, 2012) and other genes. However, there are different genes whose relationship with indicators of meat production are found, but is not fully investigated. The study of pig genome using Illumina Porcine SNP60 BeadChip were discovered single nucleotide polymorphisms (SNP) in the gene *NFE2L1* associated with the parameters of meat production (Liu *et al.*, 2015)

Nuclear factor erythroid-derived 2-related factor 1 (NFE2L1) is a member of the Cap-N-Collar (CNC) sub-family of basic leucine zipper (bZIP) transcription factors (CNC-bZIP) (Biswas and Chan, 2010; Kim, Han, & Chan, 2016). The CNC-bZIP factors play a key role in expression regulation of such iron-related genes as ferritin, P-globin and HO-1 (Igarashi *et al.*, 1998; Sun *et al.*, 2002; Chepelev, 2011). The gene *NFE2L1* codes protein, which involved in expression of globin gene (Shivdasani and Orkin, 1995). Disruption of the transcription factor NFE2L1 results in embryonic lethality and anemia in mice (Chan *et al.*, 1998; Gasiorek & Blank, 2015). Expression of *NFE2L1* gene is a key regulator in the cellular antioxidant defense system and synthesis of proteasomes enzymes (Biswas and Chan, 2010; Chepelev, 2011; Furuya*et al.*, 2014; Lisse, King, and Rieger, 2016).

High expression of *NFE2L1* gene was evaluated in bovine muscle tissue (Wang *et al.*, 2005), where it works as a part of gene regulatory networks (Reverter *et al.*, 2005). Active expression of *NFE2L1* gene was detected in muscle tissue in human (www.genevisible.com, 2014; www.gtexportal.org, 2015), mice (www.ebi.ac.uk/gxa/experiments, 2015) and Texel sheep meat breed (Jiang *et al.*, 2014). Surrounding of *NFE2L1* gene in the genome of sheep has been found many quantitative trait loci (QTL) (www.i.animalgenome.org, 2015). They are associated with resistance to parasitic diseases (Crawford *et al.*, 2006), jaw length (Beraldi *et al.*, 2007), milk production (Jonas *et al.*, 2011) and fatty acids contents in milk (García-Fernández *et al.*, 2010).

In sheep genome *NFE2L1* gene is located in chromosome 11. Up today has been found two transcription variants that differ in the number of exons. In one case, the gene has six exons, five of them are encoding (www.ncbi.nlm.nih.gov/gene, 2015). In another – seven exons, six of them are encoding (www.ensembl.org/Ovis_aries/Gene/, 2015). In the region of gene has been found 299 SNP (www.ncbi.nlm.nih.gov/snp, 2015).

There are no data of structure of *NFE2L1* gene in Russian sheep breed. In 1993 in the Russia was bred Manych Merino. It has high levels of wool productivity (up to 7.8 kg, fineness 22-27 mkm) and good meat qualities. The live weight of rams is 115-120 kg, ewes 55-56 kg. Sheep of this breed are widely used in different climatic zones in all categories of farms to improve the

breeding qualities of other breeds. Their distinctive features are good breeding characteristics and high hereditary capacity (Surov and Aboneev, 2009).

The aim of this study was to examine the *NFE2L1*gene structure to identify SNP and evaluate their relationship with indicators of meat production in sheep.

MATERIALS AND METHODS

Sample collection: Investigated Manych Merino rams (n = 30) at an age of one year from a livestock-breeding farm in Stavropol Krai, Russian Federation. In order to obtain data about the maximum number of *NFE2L1* gene alleles was selected twenty animals with maximum height (72-79 cm) and weight (59-64 kg) and ten animals of the same population with a minimum height (64-70 cm) and weight (53-56 kg). All animals were healthy and kept in optimal conditions and fed with a total mixed ration. To describe meat production analyzed parameters of body measurements.

DNA isolation: Genomic DNA was extracted from blood samples obtained from the jugular vein under aseptic conditions. Blood samples were collected in Vacutainer® vials with stabilizer EDTA (Becton Dickinson and Company, Franklin Lakes, NJ, USA) and were transported to the laboratory at +4°C within 6 hours. For DNA extractionfrom 0.2 ml of blood used the PureLink Genomic DNA MiniKit (Invitrogen Life Technologies, Grand Island, NY, USA).

Targeted enrichment and NextGeneration sequencing: In order to detect mutations in the genes, target enrichment was done and the investigated DNA fragments were sequenced. For enrichment of target regions, we used NimbleGen technology (Roche NimbleGen, Inc., Madison, WI, USA). Target regions probes were developed with Roche NimbleGen (USA). Libraries of DNA fragments from the investigated animals were prepared in accordance with the protocol in the Rapid Library Preparation Method Manual undergo the procedure of enrichment using NimbleGenSeqCap EZ Developer Libraries in accordance with the manufacturer protocol (Roche NimbleGen, Inc., Madison, WI, USA).

Monoclonal amplification of the enriched target regions of DNA was carried out according to a standard protocol in the emPCR Amplification Method Manual, Lib-L (Roche NimbleGen, Inc., Madison, WI, USA). Sequencing was performed using a GS Junior genomic sequencer (Roche NimbleGen, Inc., Madison, WI, USA). The resulting sequences were mapped to the reference genome assembly Ovis aries oviAri3 (The National Center for Biotechnology Information. Genome. (2012) Ovisaries (sheep), 2015) by GS Reference Mapper v2.9 software (Roche NimbleGen, Inc., Madison, WI, USA).

To describe a single nucleotide polymorphism (SNP) was used HGVS nomenclature (www.hgvs.org). Using of this nomenclature was based on transcript XM_004012809.2 (www.ensembl.org).

Statistical analysis: Phylogenetic analysis was performed using Unipro UGENE 1.15.1 software (Unipro, Russia).

For statistical analysis used Student's t-test in Excel for Windows statistical plug-in. Significant difference detected if $p<0.05$.

RESULTS

In this work analyzed effect of polymorphisms of the *NFE2L1* gene on body parameters in sheep. During sequencing was found eleven single nucleotide polymorphisms (SNP) in exons area and regulatory regions of the*NFE2L1* gene. Five SNPs were detected for the first time: c.*179C>T, c.*181C>A, c.*182G>T, c.*187G>T and c.*188G>T. Depending on the embodiment transcription they get either in 3'UTR region of exon 6, or in 3'flanking region (Table 1 and 2.). The predominant percentage of detected point mutations account for transitions, more likely to change purine nucleotides. One of the found replacements, c.788C>T leads to a change in the sequence of amino acid chain. In codon number 263 alanine amino acid is replaced by valine.

Located in the coding part of exons SNPs c.582C>T, c.788C>T and c.864C>T are presented only as heterozygotes. Located in 3'UTR region SNP are more common in homozygous form. New SNP c.*187G>T and c.*188G>T are detected in the genome of studied animals only as homozygotes. The most common SNP are c.*177C>G and c.*179C>T. They are presented in homozygous form in 28 of 30 tested animals. Very rare SNP is c.*187G>T, it is found in genome of one studied animal only.

Phylogenetic analysis shown 12 variants of the *NFE2L1* gene according to eleven detected SNP. Investigated animals per totality of identify mutations have been divided into three main groups A, B and C (Table 2.). Groups A and C consists five subgroups, group B – two subgroups.

To assess the effect of the *NFE2L1* gene polymorphisms on the meat production parameters in Manych Merino sheep breed choses four SNP: c.-1092 (in 5'UTR), c.788 (in 4 exon), c.864 (in 5 exon) and c.*188 (in 3'flanking region). In animals with a heterozygous genotype for SNP c.-1092 only two parameters of lifetime productivity evaluation indicators differed from the mutant homozygotes. Heterozygotes have live weight less than 8%, and chest depth - less than 3% compared to wild homozygotes. The impact of mutations on the other indicators could not been identified (Table 3.). Also, the presence in the gene SNP c.864 in heterozygous variant was not associated with

changes in the external measurements in sheep compared to animals with wild homozygous genotype (Table 3.).

Comparison between animals with wild homozygous and heterozygous genotypes for SNP c.788 showed that live weight in heterozygotes was significantly lower at 8.4%. Heterozygous type carriers of SNP was significantly lower in height at croup by 4.4%, carcass length by 4%, chest depth by 3.6% and metatarsus length by 7.6%. Other parameters did not differ significantly among themselves and did not depend on the presence of the gene allele (Table 4.).

The presence in the genotype of SNP c.*188 in heterozygous variant resulted in a significant increase in live weight at 6.4%, height at wither at 5.3%, height at croup at 5.6%, chest depth by 3.1% and loin width by 5.5%(Table 4.). The other parameters of productivity between the two groups did not differ significantly.

Table 1.The frequency of the *NFE2L1* gene polymorphic alleles in Manych Merino sheep breed.

	Name of SNP in HGVS nomenclature	Position in contig	Identifier in the NCBI database	Allele		Genotype		
1	c.-1092T>C	37981597	rs419341931	A	G	AA	AG	GG
				0.37	0.63	0.00	0.73	0.27
2	c.-703C>T	37981208	rs161072121	G	A	GG	GA	AA
				0.33	0.67	0.00	0.67	0.33
3	c.582C>T	37975254	rs424623129	G	A	GG	GA	AA
				0.67	0.33	0.33	0.67	0.00
4	c.788C>T	37974631	rs412034526	G	A	GG	GA	AA
				0.73	0.27	0.47	0.53	0.00
5	c.864C>T	37974332	rs162134364	G	A	GG	GA	AA
				0.87	0.13	0.73	0.27	0.00
6	c.*177C>G	37971899	rs161071979	G	C	GG	GC	CC
				0.03	0.97	0.00	0.07	0.93
7	c.*179C>T	37971897	Notindatabase	G	A	GG	GA	AA
				0.07	0.93	0.07	0.00	0.93
8	c.*181C>A	37971895	Not in database	G	T	GG	GT	TT
				0.43	0.57	0.33	0.20	0.47
9	c.*182G>T	37971894	Not in database	C	A	CC	CA	AA
				0.80	0.20	0.74	0.13	0.13
10	c.*187G>T	37971889	Not in database	C	A	CC	CA	AA
				0.93	0.07	0.93	0.00	0.07
11	c.*188G>T	37971888	Not in database	C	A	CC	CA	AA
				0.73	0.27	0.73	0.00	0.27

Table 2.The *NFE2L1* gene genotypes identified in Manych Merino sheep breed. Homozygous mutant allele is indicated black, heterozygous - gray, homozygous wild-type allele – white.

Number of animals	Genotype		*SNP*										
			1 intron/5'UTR c.-1092		3 exon	4 exon	5 exon	3'UTR/3'flanking					
			c.-703	c.582	c.788	c.864	c.*177	c.*179	c.*181	c.*182	c.*187	c.*188	
2	A	1	■	■	□	□	▒	■	□	□	▒	□	■
2		2	▒	▒	▒	□	□	■	■	□	■	□	■
2		3	▒	▒	▒	▒	□	■	■	□	□	□	■
2		4	■	■	□	□	□	■	■	□	▒	□	■
2		5	▒	▒	▒	▒	□	■	■	□	□	□	□
2	B	1	■	■	□	□	□	■	■	▒	□	□	□
4		2	▒	▒	▒	▒	□	■	■	▒	□	□	□
2	C	1	▒	▒	▒	▒	□	■	■	■	□	□	□
4		2	▒	▒	▒	▒	▒	■	■	■	□	□	□
4		3	□	■	▒	□	▒	■	■	■	□	□	□
2		4	■	■	□	□	▒	■	■	■	□	■	□
2		5	▒	▒	□	□	□	▒	■	■	□	□	□

Table 3. Body measurements of rams with different *NFE2L1* genotypes (n represents number of animals; W represents wild type allele; Mu represents mutant allele; significantly different from wild type homozygotes if p<0.05).

Sr. No.	Trait	Genotype					
		c.-1092			c.864		
		W/Mu, (M±m, n=22)	Mu/Mu, (M±m, n=8)	p Value	W/W, (M±m, n=22)	W/Mu, (M±m, n=8)	p Value
1.	Live weight (kg)	56.55±0.94	61.40±1.17	0.01	58.26±1.11	56.70±2.09	0.49
2.	Height at wither (cm)	72.09±1.26	74.25±0.55	0.12	73.04±1.22	71.11±1.49	0.28
3.	Height at croup (cm)	74.73±0.98	75.75±1.19	0.48	75.64±0.91	73.25±1.19	0.12
4.	Width at croup (cm)	20.03±0.62	19.75±0.73	0.79	19.73±0.51	20.50±1.53	0.61
5.	Length of croup (cm)	24.09±0.36	24.25±0.87	0.86	24.36±0.35	23.50±0.75	0.29
6.	Carcass length (cm)	85.18±0.83	86.50±1.80	0.49	85.73±0.87	85.01±1.70	0.68
7.	Chest width (cm)	26.82±0.60	28.10±0.47	0.12	27.05±0.63	27.50±0.33	0.47
8.	Chest depth (cm)	31.27±0.29	32.25±0.29	0.02	31.64±0.29	31.25±0.55	0.52
9.	Chest girth (cm)	101.73±0.93	105.04±1.63	0.10	102.18±0.96	103.75±2.18	0.49
10.	Metacarpal girth (cm)	9.73±0.20	10.25±0.29	0.14	9.82±0.19	10.75±0.99	0.36
11.	Metacarpal length (cm)	14.91±0.26	16.00±1.15	0.36	15.04±0.24	15.75±1.28	0.55
12.	Metatarsus length (cm)	16.82±0.31	18.08±0.82	0.20	17.09±0.26	17.25±1.19	0.89
13.	Loin width (cm)	13.45±0.17	13.50±0.33	0.90	13.55±0.17	13.25±0.29	0.36
14.	Width of back (cm)	22.91±0.30	24.25±0.55	0.06	23.45±0.33	23.25±0.99	0.83
15.	Half girth of back (cm)	70.91±0.96	72.50±2.33	0.51	71.03±0.77	72.25±3.07	0.68

Table 4. Body measurements of rams with different *NFE2L1* genotypes (n represents number of animals; W represents wild type allele; Mu represents mutant allele; significantly different from wild type homozygotes if p<0.05).

Sr. No.	Trait	Genotype					
		c.788			c.*188		
		W/W, (M±m, n=14)	W/Mu, (M±m, n=16)	p Value	W/W, (M±m, n=22)	W/Mu, (M±m, n=8)	p Value
1.	Live weight (kg)	**60.57±0.9**	**55.46±0.91**	**0.001**	**57.32±1.17**	**61.03±0.47**	**0.01**
2.	Height at wither (cm)	74.43±1.08	70.75±1.35	0.04	**71.73±1.09**	**75.50±1.37**	**0.04**
3.	Height at croup (cm)	**76.71±1.12**	**73.38±0.67**	**0.02**	**74.09±0.62**	**78.25±1.52**	**0.04**
4.	Width at croup (cm)	19.43±0.46	20.38±0.88	0.33	20.18±0.66	19.50±0.32	0.34
5.	Length of croup (cm)	24.43±0.57	23.88±0.37	0.40	24.18±0.31	24.25±0.87	0.94
6.	Carcass length (cm)	**87.43±1.18**	**83.88±0.37**	**0.02**	85.64±0.92	86.03±0.82	0.75
7.	Chest width (cm)	26.82±0.60	28.10±0.47	0.12	27.05±0.63	27.50±0.33	0.47
8.	Chest depth (cm)	**31.27±0.29**	**32.25±0.29**	**0.02**	31.64±0.29	31.25±0.55	0.52
9.	Chest girth (cm)	101.73±0.93	105.04±1.63	0.10	102.18±0.96	103.75±2.18	0.49
10.	Metacarpal girth (cm)	9.73±0.20	10.25±0.29	0.14	9.82±0.19	10.75±0.99	0.36
11.	Metacarpal length (cm)	14.91±0.26	16.00±1.15	0.36	15.04±0.24	15.75±1.28	0.55
12.	Metatarsus length (cm)	16.82±0.31	18.08±0.82	0.20	17.09±0.26	17.25±1.19	0.89
13.	Loin width (cm)	13.45±0.17	13.50±0.33	0.90	13.55±0.17	13.25±0.29	0.36
14.	Width of back (cm)	22.91±0.30	24.25±0.55	0.06	23.45±0.33	23.25±0.99	0.83
15.	Half girth of back (cm)	70.91±0.96	72.50±2.33	0.51	71.03±0.77	72.25±3.07	0.68

DISCUSSION

The study demonstrates considerable variability the *NFE2L1* gene and relation of the gene structure and body size in Manych Merino sheep breed. Since in Russia genotyping of sheep have not been conducted, information about the structure of the *NFE2L1* gene in Manych Merino breed has obtained for the first time.

The NCBI (http://www.ncbi.nlm.nih.gov/snp, 2015) and Ensembl (http://www.ensembl.org/Ovis_aries/Gene/Variation_Gene, 2015) databases consists information about six of eleven single nucleotide

polymorphisms (SNP) that hasbeen found in the Manych Merino breed. The most common of detected SNP is c.*177C>G (rs161071979). It is represented in the genome of all animals, preferably, the mutant homozygous form. The frequency of mutant allele A is 97%. Unfortunately, the information on the prevalence of the SNP of other sheep breeds in the database is not represented.

Replacements c.-1092T>C and c.-703C>T are widespread in the genome in the Manych Merino and other breeds of sheep. The mutant allele G in locus c.-1092 found in Russian breed of sheep in 63% of cases, which is 11% less than that of Iranian and 14% less than that of Moroccan sheep. The mutant allele A in locus c.-703 inManych Merino found in 67%, which is 3% less than the Iranian and 6% less than the Moroccan sheep breeds (www.ensembl.org/Ovis_aries/Gene, 2015). Detected SNP c.-1092T>C and c.-703C>T found in the genome of all investigated animals both in heterozygous and in the mutant homozygous form.

Synonymous SNP c.582C>T and missense mutation c.788C>T in Manych Merino breed are found in the heterozygous formonly. The frequency of the mutant allele A in Manych Merino in c.582 locus is 33% and higher than that of the Iranian sheep breeds 1.7 folds, Moroccan - 2.4 folds. In the locus c.788 frequency of mutant allele is 27%, which is 1.5 folds higher than that in Iranian sheep and 2.25 folds than in Moroccan (www.ensembl.org/Ovis_aries/Gene/Variation_Gene, 2015).

This studies about the influence of individual SNP and their combinations on the lifetime productivity indicators of Manych Merino breed of sheep showed that these parameters affected by the SNP, located both in the coding and noncoding regions of the *NFE2L1* gene. Found in exon4 nonsynonymous SNP c.788, leading to a change in the amino acid sequence (alanine is changed to valine), significantly changes the physiological properties of the protein. It is appeared in a negative impact on the productive performance of the surveyed sheep even with the replacement in the heterozygous form. The selection should take into account the impact of the presence of SNP c.788 in the genome and by directed mating reduce number of heterozygotes in the population.

Located in exon 5 SNP c.864 is synonymous, and is not caused amino acid replacements, that determined the lack of link between its availability and productive qualities of animals. Detected SNP c.-1092, the most far located in the 5' direction from the first exon among identified SNP influenced mainly on the parameter of live weight with virtually unexpressed difference in the size of the animals. Perhaps a deeper analysis of slaughtered meat production indicators can detect the connection between this SNP with any group of parameters. An important characteristic of the SNP c.-1092 is the absence of wild homozygous genotype in the group of investigated animals, which may be an indication of the sequential elimination of wild allele during breeding.

The most pronounced effect on the lifetime performance efficiency in Manych Merino had SNP of c.*188 located at the opposite end of the nucleotide sequence of the gene, and most remote environments has been found in the 3' direction. This SNP occurs only in the homozygous form among animals examined - either wild or mutant. Apparently, heterozygous variant carriers showed a high enough capacity to breed and have been culled in the course of breeding.

From the four SNP, which effect on the body parameters of Manych Merino sheep breed was studied the one SNP had a negligible effect on the lifetime performance. Next one SNP in the heterozygous variant reduces the productivity indicators; one SNP affects only two options. Only one SNP - c.*188 has a positive effect on a number of parameters of meat production and can be used as a genomic marker for selection work.

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