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STUDY OF GENETIC ARCHITECTURE OF FEED CONVERSION RATE IN DUROC YOUNG BOARS (*Sus scrofa*) BASED ON THE GENOME-WIDE SNP ANALYSIS

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Abstract

Feed conversion (feed conversion ratio — FCR, kg/kg), calculated as the ratio of the amount of feed intake to the body weight gain, is the most important trait that determines the economic efficiency of pork production. The development of automated feeding stations allows researchers to carry out an accurate individual measurements of feed intake in the group-housed pigs, which became the basis for the integration of the FCR in the breeding programs. The development of high-throughput genotyping methods for tens of thousands of single-nucleotide polymorphisms (SNPs) made it possible to identify genetic factors associated with economically important animal traits at genome-wide level. Previous studies, performed in different pig breeds have shown the presence in the genome of the pig of multiple QTLs for FCR, while the regions of the genome identified in different studies were only partially overlapped. In this report, we present the genome-wide association studies results in one of the Russian Duroc boar population, which revealed the presence of 30 SNPs that were significantly associated with the feed conversion rate, as well as positional and functional candidate genes whose products are involved in the regulation of proliferation and differentiation various types of cells in lipid hematopoiesis and metabolism. The aim of the present work was to study the genetic factors affecting the feed efficiency in Duroc young boars, phenotyped individually for feed conversion rates and genotyped by ~ 70 thousand single-nucleotide polymorphisms at the genome-wide level. The study was performed on 715 young Duroc boars marked with electronic chips. Individual values of feed intake were recorded using automatic feeding stations MLP-RAP («Schauer Agrotronic AG», Switzerland) and GENSTAR («Cooperl Arc Atlantique», France). Genotyping was performed using a high-density DNA chip GGP Porcine HD (GeneSeek Genomic Profiler platform, Neogene, USA) containing of ~ 70 thousand SNPs. After quality control, 44810 SNPs were selected for genome-wide association studies (GWAS). Average daily gain (ADG) in the studied pigs amounted to 962.04±5.06 g/day, and feed conversion (FCR) was 2.53±0.2 kg/kg. Based on the GWAS analysis, 30 significant ($p < 0.00001$) SNPs localized at SSC2, SSC3, SSC4, SSC6, SSC7, SSC12 and SSC15 were identified, including three genome-wide significant SNPs, the H3GA0010441 ($p < 4.14\times10^{-7}$), ALGA0119936 ($p < 1.03\times10^{-6}$) on SSC3, and ASGA0028727 ($p < 1.17\times10^{-6}$) on SSC6. At SSC2, SSC6 and SSC15, the SNPs' blocks, consisting 10 (in the region of 29.0-30.9 cM, Sscrofa genome assembly 10.2), 7 (79.1-80.3 cM) and 3 SNPs (69.3-70.7 cM), respectively, were identified. Annotation of candidate genes localized in close proximity to significant SNPs revealed genes whose products are involved in heterogeneous biological processes, such as regulation of proliferation and differentiation of different cell types, hematopoiesis, lipid

metabolism. The additional studies aimed at validation of detected associations in other populations of pigs are necessary. Identification of novel QTLs for feed conversion rate will enhance our understanding of the genomic architecture of this important breeding trait.

Keywords: genome-wide association studies, feed conversion rate, average daily gain, back fat, Duroc boars.

Increasing productivity while reducing feed costs is one of the main goals in farm animal breeding [1, 2]. The feed conversion ratio (FCR), calculated as the ratio of the amount of eaten feed to the increase in live bodyweight, is the most important indicator that determines the economic efficiency of pork production, since the costs of feed reach 70% of the prime cost of pork [3, 4]. The development of automated feed stations made it possible to conduct accurate individual measurements of feed intake in group-housed pigs, which became the basis for integrating the FCR indicator into the breeding programs [5-7]. A detailed analysis of the heritability of feed conversion, conducted on three breeds of pigs [8], revealed a moderate genetic variation between individual breeds (h^2 = 0.30-0.54). The individual differences in feed conversion, based on genetic factors, allow identification of DNA markers of the trait in order to predict this indicator and to use it in pig breeding [9-13].

Based on the analysis of the genetic linkage of microsatellite markers, a number of QTLs were identified for the feed conversion indicator [14]. Thus, in the crossbred population (Meishan × Large White), QTLs for FCR were detected on SSC11 and SSC14 [15]. In the F_2 resource population (White Duroc × Erhual), using 183 microsatellites, 3 QTLs for FCR were found on SSC2, SSC7 and SSC9 [16]. The study of the Large White × Pietrain resource population for 118 microsatellite markers revealed the QTLs for FCR on SSC7 [17]. Mapping with 88 informative microsatellites performed in a crossbred pig population revealed the presence of QTLs for FCR on SSC2, SSC6 and SSC7 (for a feeding period from 90 to 120 kg) and on SSC2, SSC4 and SSC14 (for a feeding period from 60 to 140 kg) [18]. However, most QTLs, identified based on linkage analysis, were characterized by relatively low localization accuracy (in the range of more than 20 cM).

Improving the accuracy of QTL mapping and identification of the corresponding DNA markers became possible due to a DNA chip that allows the simultaneous analysis of tens of thousands of SNPs (Porcine60K BeadChip, Illumina, Inc., USA). In Duroc pigs, the presence of regions reliably associated with FCR was found on SSC4, SSC7, SSC8 and SSC14 [19], on SSC4 and SSC15 [20], and on SSC12 [21]. A genome-wide association study (GWAS) of the F_2 resource population showed the presence of QTL for FCR on SSC7 [22]. Maxgro terminal boars have 12 1-Mb regions on SSC6, SSC7, SSC9, SSC11, SSC14 and SSC15, responsible for more than 0.5% of the genetic variation of the trait [23]. Thus, the previous works showed the presence of multiple QTLs in the pig genome associated with feed conversion, while the parts of the genome, identified in different works, overlapped only partially. The involvement of new pig populations in the research expands the understanding of the genomic architecture of this important breeding trait.

This paper is the first to report data on the genetic conditionality of the inheritance of a complex and economically significant breeding indicator, the feed conversion, obtained with the use of microarray technology on a pig population of Russian reproduction. In this report, we present the results of genome-wide association analysis in one of the Russian populations of Duroc boars, phenotyped individually for feed conversion and genotyped for ~ 70 thousand single nucleotide polymorphisms (SNPs) at the genome-wide level. As a result, 30

SNPs were identified that were reliably associated with the feed conversion indicator, as well as positional and functional candidate genes the products of which are involved in the regulation of proliferation and differentiation of various types of cells, in hematopoiesis and lipid metabolism.

The subjective of the work was to study the genetic factors affecting the efficiency of feed use in Duroc boars.

Techniques. The studies were conducted in OOO "SGTs" (Voronezh Province, Verkhnyaya Khava settlement) from October 2017 to November 2018 on 715 Duroc boars labeled with electronic chips. The tissue samples (ear pluck) were collected from all animals, preserved with 96% alcohol and stored at –20 °C. The average age of the animals at the beginning and the end of the experiment was 77.6±0.3 and 156.2±0.4 days, respectively. The boars were kept at the quarters with slotted floors in groups of 15 animals each (floor area 1.30 m^2/animal) at 18 °C. The animals had unlimited access to food and water. Feed consumption was individually measured using automatic feed stations MLPII-RAP (Schauer Agrotronic AG, Switzerland) and GENSTAR (Cooperl Arc Atlantique, France).

The FCR value was calculated for each animal as the ratio of the eaten feed to the increase in live bodyweight over the entire growing period. The values for the parameters of the initial and final weight of the boars, daily average weight gain and duration of testing at the stations were checked for compliance with the normal distribution ($M \pm 3\sigma$). Given the differences in the duration of the growing period between the groups, the heterogeneity of the formation of groups of animals by live weight (both when setting and removing from fattening), as well as the rate of growth, to obtain comparable feed conversion values, was assessed using the multiple linear regression equation of the FCR indicator, calculated with STATISTICA 10 (StatSoft, Inc., USA):

$$FCR_{(r)} = 4.6738 - 0.0158x_1 - 0.0170x_2 + 0.0183x_3 - 0.0024x_4,$$

where $FCR_{(r)}$ is the regression value of feed conversion; x_1 is the duration of the feeding period at the station; x_2 is live weight at the beginning of fattening; x_3 is live weight at the end of fattening; x_4 is the average daily gain in live weight over a period; 4.6738 is a free member of the equation, a constant value.

To isolate DNA from the tissue samples, the DNA Extran 2 kit (OOO NPF Syntol, Russia) was used in accordance with the manufacturer's recommendations. The concentration of double-stranded DNA was determined using a Qubit 2.0 fluorimeter (Invitrogen/Life Technologies, USA). OD_{260}/OD_{280} ratio was measured (NanoDrop8000 spectrophotometer, Thermo Fisher Scientific, USA) to determine the DNA quality. DNA with OD_{260}/OD_{280} = 1.6-1.8 was used in the analysis. In addition, the DNA quality was evaluated by gel electrophoresis on a 1% agarose gel.

Genome-wide genotyping was performed with a high-density DNA chip Porcine GGP HD (GeneSeek Genomic Profiler platform, Neogene, USA) containing ~ 70 thousand SNPs. Quality control and filtering of genotyping data for each SNP and each sample was performed with the PLINK 1.9 software package (http://zzz.bwh.har-vard.edu/plink/) applying the following filters (the corresponding commands in the PLINK program are given in brackets): the quality of genotyping for all studied SNPs for an individual is not lower than 90% (--mind); the quality of genotyping for each of the studied SNPs in all individuals is not less than 90 % (--geno); the frequency of occurrence of minor alleles (MAF) is 0.03 (--maf); deviation of SNP genotypes from the Hardy-Weinberg distribution in the aggregate of tested samples with a p-value $< 10^{-6}$ (--hwe). After the quality control, 44,810 SNPs were selected for GWAS analysis.

Regression analysis in the PLINK 1.90 (--assoc --adjust --qt-means) was used to identify associations of SNP markers with the FCR indicator. To

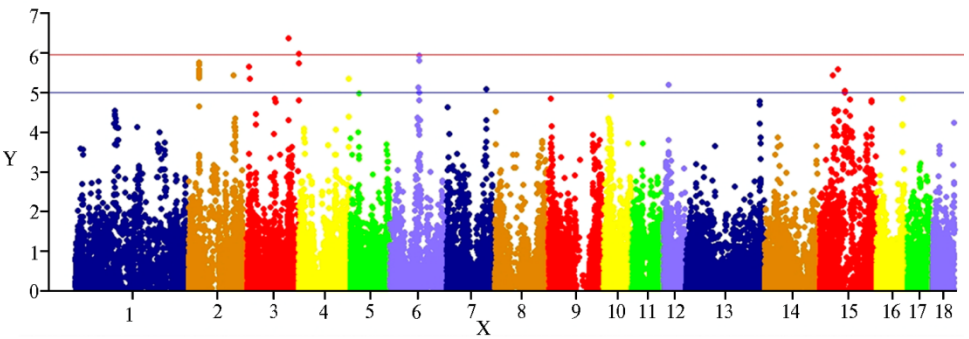
confirm the reliable effect of SNP and to determine significant regions in the pig genome, we tested the Bonferroni null hypotheses at a threshold value of $p < 1.12\times10^{-6}$, $^{0.05}/_{44,810}$. The data was visualized in the qqman package using the programming language R [24]. To search for candidate genes localized in the region identified by SNP, the genomic resource Sscrofa10.2 was used (https://www.ncbi.nlm.nih.gov/assembly/GCF_000003025.5/, reference date of April 2, 2019). Functional gene annotations were performed using the GeneCards database (http://www.genecards.org/, reference date of April 2, 2019). The arithmetic mean (*M*), the standard error of the mean (±SEM), and the coefficient of variation (*Cv*, %) were calculated with MS Excel 2013.

Results. The initial and final live weight of the boars used in the studies was 35.3±0.2 and 110.5±0.5 kg, respectively, with daily average gain over the control period of 962.0±5.1 g and the average feed conversion of 2.53±0.02 kg/kg (Table 1).

1. Phenotypic indicators in the studied sample of Duroc boars (*Sus scrofa*) (*n* = 715, OOO SGTs, Voronezh Province, Verkhnyaya Khava settlement, October 2017-November 2018)

Indicator	*M*±SEM	Min	Max	C_V, %
Initial live weight, kg	35.3±0.2	19.9	53.0	15.7
Final live weight, kg	107.3±0.5	75.0	157.0	10.9
ADG, g/day	962.0±5.1	547.5	1507.7	14.0
ADFI, g/day	2411±15	1318	3762	16.4
FCR, kg/kg	2.53±0.02	1.33	4.03	16.2

N o t e. ADG, g/day — daily average gain; ADFI, g/day — average daily feed intake; FCR, kg/kg — feed conversion; *M* — mean value; SEM — error of the mean; Min — minimum value, Max — maximum value; C_V, % — coefficient of variation (the ratio of the standard deviation σ of a random variable to its expected value).



GWAS analysis for the feed conversion indicator in the studied sample of Duroc boars (*Sus scrofa*): X-axis — the chromosome number; Y-axis — the inverse decimal logarithm of the confidence level $-\log_{10}(p)$; upper horizontal line — confidence threshold for genome-wide associations $-\log_{10}(p) = 1.2\times10^{-6}$; lower horizontal line — confidence threshold for suggestive associations $-\log_{10}(p) = 1.02\times10^{-5}$ (*n* = 715, OOO SGTs, Voronezh Province, Verkhnyaya Khava settlement, October 2017-November 2018).

Using GWAS analysis, we identified 30 SNPs on SSC2, SSC3, SSC4, SSC6, SSC7, SSC12 and SSC15, which were reliably associated with the FCR indicator ($p < 0.00001$), while blocks from 3-10 SNPs were found on SSC2, SSC6 and SSC15. For three SNPs (H3GA0010441, ALGA0119936 on SSC3 and ASGA0028727 on SSC6), the confidence level exceeded the threshold for genome-wide studies ($p < 1.2\times10^{-6}$) (Fig., Table 2).

The most interesting positional and functional candidate genes identified in close proximity to significant SNPs include the *ABTB2*, *CAPRIN1* (located on SSC3 inside a block of 10 SNP candidates in the 29.0-30.9 cM region), *RBAK* (located on SSC3 in the immediate vicinity, –10825, from the genome-wide SNP ALGA0119936), *PTPRU, MECR, MED18, PHACTR4* and *RCC1* (located on SSC6 inside a block of 7 SNP candidates in the 79.1-80.3 cM region).

2. Reliably significant ($p < 0.00001$) SNPs associated with feed conversion in Duroc boars (*Sus scrofa*), and candidate genes (n = 715, OOO SGTs, Voronezh Province, Verkhnyaya Khava settlement, October 2017-November 2018)

SSC	SNP number	SNP	Position	p	Candidate gene (position)
2	10	INRA0059415	28977392	2.57×10^{-6}	*ABTB2* 28,946,563 ... 29,149,547; *NAT10*
		ASGA0082316	29159639	2.84×10^{-6}	29,153,541 ... 29,194,433; *CAPRIN1* 29,199,142 ...
		ALGA0012786	29501376	3.92×10^{-6}	29,242,779; *LMO2* 29,401,270 ... 29,422,801;
		WU_10.2_2_30191053	30191053	2.00×10^{-6}	*KIAA1549L* 29,617,451 ... 29,746,696; *CD59*
		ASGA0097788	30337163	4.32×10^{-6}	29,777,121 ... 29,797,735; *FBXO3* 29,800,868 ...
		WU_10.2_2_30595322	30595322	3.19×10^{-6}	29,812,278; *HIPK3* 30,028,373 ... 30,057,948;
		WU_10.2_2_30650235	30650235	3.19×10^{-6}	*DEPDC7* 30,336,221 ... 30,344,776; *TCP11L1*
		ALGA0012822	30781606	2.01×10^{-6}	30,353,850 ... 30,399,032; *CSTF3* 30,402,895 ...
		ASGA0009813	30860286	1.72×10^{-6}	30,418,796; *QSER1* 30,443,575 ... 30,528,992;
		ALGA0012826	30894959	3.28×10^{-6}	*PRRG4* 30,549,353 ... 30,569,161; *CCDC73* 30,598,386 ... 30,748,173; *EIF3M* 30,748,559 ... 30,772,863; *WT1* 30,902,160 ... 30,946,266
	1	ALGA0015465	124437922	3.73×10^{-6}	*CCDC112* 124,337,488 ... 124,341,509; *TICAM2* 124,610,898 ... 124,613,028; *TMED7* 124,682,078 ... 124,691,898
3	1	H3GA0008543	7379529	2.24×10^{-6}	*LAMTOR4* 7,350,308 ... 7,402,741
	1	WU_10.2_3_8562889	8562889	4.56×10^{-6}	*COL26A1* 8,559,750 ... 8,703,022; *MYL10* 8,726,761 ... 8,738,595
	1	H3GA0010441[a]	116920902	4.14×10^{-7}	*CLIP4* 116,931,705 ... 117,021,159
	2	WU_10.2_3_144118805	144118805	1.83×10^{-6}	*RBAK* 144,137,154 ... 144,154,400
		ALGA0119936[a]	144165225	1.03×10^{-6}	
4	1	WU_10.2_4_140678150	140678150	4.40×10^{-6}	*LMO4-201* 141,341,709...141,354,291
6	7	WU_10.2_6_79124865	79124865	7.22×10^{-6}	*MED18* 79,123,55...79,156,756; *PHACTR4*
		WU_10.2_6_79310063	79310063	7.22×10^{-6}	79,256,482...79,343,715; *RCC1*
		ASGA0087502	80148516	9.87×10^{-6}	79,351,068...79,378,340; *TRNAU1AP*
		ASGA0028727[a]	80164977	1.17×10^{-6}	79,381,689...79,406,923; *RAB42*
		ALGA0035788	80216205	1.57×10^{-6}	79,417,316...79,419,319; *TAF12*
		ALGA0114520	80246537	1.57×10^{-6}	79,432,412...79,441,136; *YTHDF2*
		WU_10.2_6_80303210	80303210	1.57×10^{-6}	79,553,445...79,583,689; *OPRD1* 79,611,950...79,662,042; *EPB41* 79,809,404...79,916,611; *TMEM200B* 79,916,247...79,920,674; *SRSF4* 79,952,072...79,979,921; *MECR* 79,986,968...80,018,140; *PTPRU* 80,024,234...80,106,252
7	1	H3GA0022804	109049333	7.98×10^{-6}	*DIO2* 109,299,323...109,308,576
12	1	WU_10.2_12_15902684	15902684	6.47×10^{-6}	*MARCH10* 15,861,982...15,944,352
15	1	MARC0002947	35674169	3.69×10^{-6}	*PTPN18* 35,772,241...35,792,658
	1	DRGA0015116	50414290	2.54×10^{-6}	*TENM3* 50,292,659...50,995,047
	3	H3GA0044471	69276645	1.02×10^{-5}	*KCNJ3* 69,329,216...69,481,280; *NR4A2* 70,671,034 ... 70,689,181; *GPD2* 70,841,147...70,946,575
		H3GA0044472	69300270	9.18×10^{-6}	
		ALGA0085736	70725225	9.18×10^{-6}	

N o t e. [a] is SNPs with a confidence level that exceeds the threshold for genome-wide associations. The positions in the assembly of the Sscrofa10.2 genome are indicated (https://www.ncbi.nlm.nih.gov/assembly/GCF_000003025.5/).

The product of *ABTB2* has activity of protein heterodimerization, the product of *CAPRIN1* is involved in the regulation of proliferation and migration of various cell types. The protein encoded by *LMO2* plays a central role in the development of hematopoiesis, the protein encoded by *RBAK* interacts with the androgen receptor which affects cell proliferation and differentiation, as well as with the transcription factor E2F which plays a crucial role in the control of the cell cycle. PTPRU is a signaling molecule that regulates a wide range of cellular processes, including growth, differentiation, and the mitotic cycle. Among the known functions of *MECR* is participation in the metabolism and biosynthesis of fatty acids. The *MED18* product, a component of the mediator complex, is involved in the regulation of transcription, and its participation in lipid metabolism has also been established. The functions of the protein encoded by *PHACTR4* include participation in the proliferation of nervous cells, as well as interaction with the α-actin of the skeletal muscles, which are involved in motility of different cell types. In humans, a relationship is established between polymorphisms in the *CAPRIN1*, *LMO2*, *MECR*, *PTPRU*, *PHACTR4* and *RCC1* genes with sys-

tolic pressure, in *LMO2*, *PTPRU* and *ABTB2* — with the blood protein concentration, in *CAPRIN1*, *LMO2*, *MED18*, *PHACTR4* and *RBAK* — with parameters of erythrocytes. It is known that the level of systolic pressure is associated with the growth rate in the juvenile period [25]. In turn, a relationship was established between the hematological parameters and the growth rate of pigs [26, 27], which, as is known, correlates with feed conversion [5]. The relationship is shown between the protein (glycoprotein and haptoglobin) content in the blood of pigs and the growth rate and the efficiency of feed use [28].

Thus, the conducted genome-wide studies of the Duroc boar population revealed 30 SNPs reliably associated with the feed conversion index and located on SSC2, SSC3, SSC4, SSC6, SSC7, SSC12 and SSC15 ($p < 0.00001$), with blocks of 3-10 SNPs found on SSC2, SSC6, and SSC15. The analysis of genomic regions with reliable SNPs shows several positional and functional candidate genes, the products of which are involved in the regulation of proliferation and differentiation of various cell types, hematopoiesis, and lipid metabolism. Further studies are required to validate the associations found in other pig populations. Identification of QTLs based on feed conversion expands understanding of the genomic architecture of this crucial breeding trait.

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