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GENOME-WIDE ASSOCIATION STUDIES OF GROWTH DYNAMICS IN QUAILS *Coturnix coturnix*

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Abstract

Identification and mapping genes that determine economically important traits in farm animals, including poultry, is a key task of genomic selection aimed at improving the efficiency of animal husbandry. In recent years, genome-wide association studies have identified many important candidate genes in various farm animals. Of poultry species, a significant proportion of studies on the search and identification of quantitative trait loci (QTL) was carried out on chickens. On quails, such studies are relatively few primarily due to the lack of commercial chips, which makes it difficult to search for SNPs and identify genes associated with valuable traits. To date, there is little information on the quantitative traits loci reliably associated with productivity performance of quails. The meat productivity of quails, e.g., bodyweight and growth rate, depend on feeding and keeping conditions and is genetically determined by a set of QTL. This report submits the results of a genome-wide association study of the growth rate of F_2 quails in a model resource population. We aimed to identify the QTL in the quail genome, to analyze the association of the found mutations with body weight parameters, and to characterize allelic variants in the studied F_2 quail population. The F_2 model resource population was obtained by crossing two breeds, the Japanese quails with a slow growth and the Texas quails with a fast growth. After filtering the data of GBS genotyping of the obtained F_2 individuals (n = 232), the 92686 SNPs were selected for further analysis. We used PLINK 1.9 software (https://www.cog-genomics.org/plink/) options geno 0.1, mind 0.2, and maf 0.05 to analyze the associations of whole genome genotyping data with the bodyweight which reflects growth and development of birds. High variability of bodyweight was found to be typical of the created resource population. In 1-day-old quails, this indicator varied from 5 to 11 g and averaged 9±0.1 g. At the age of 2, 4, 6, and 8 weeks, the bodyweight reached 69±1, 157±2, 219±2 and 252±2 g, respectively. GWAS identified 149 SNPs that were associated with bodyweight at a high statistical significance ($p < 0.00001$).These SNPs are located on chromosomes 1, 2, 3, 5, 6, 8, 11, 14, 15, 20, 24, 25 and 26. On chromosomes 1, 2, 3, 5, 11 and 26, there were blocks of 2-9 SNPs linked to the same gene. Seven candidate genes (*PCDH9*, *SMAD9*, *PAN4*, *EGFR*, *WDPCP*, *MDGA2*, and *PEPD*) were identified that were associated ($p < 0.00001$) with bodyweight of quails at 8 weeks of age. We intend to further study the detected SNPs as genetic markers in breeding quails for an increased bodyweight. Additionally, associations of these SNPs with other parameters of growth intensity and productivity performance in quails will be under consideration.

Keywords: *Coturnix japonica*, quail, QTL, SNP, GBS, GWAS, bodyweight, growth dynamics

Poultry meat and eggs, which today constitute a significant share of the total livestock production in the world [1, 2], are mainly produced using species belonging to the *Phasianidae* family. Quail products are in special demand, which is explained by the high nutritional value and taste of quail eggs and meat, as well as their precocity [3-5]. The market demand for these products contributed to the creation of large quail farms and the intensive development of the industry, as a result, quail eggs and meat have become everyday products. The profitability and competitiveness of quail farming are due to several reasons. One of the determining factors is the use of breeds and lines of poultry, which are characterized by important breeding traits, which include high egg and meat productivity, resistance to industrial stresses, infectious diseases, and precocity. The creation of highly productive breeds, lines and crosses is impossible without effective breeding work to search for and identify valuable genotypes using modern methods and approaches based on the study of the molecular genetic mechanisms of the formation and manifestation of selectively significant traits.

Thousands of quantitative trait loci (QTL) have now been identified in farm animals for a significant number of economically useful traits [6]. Of the numerous poultry species, a significant proportion of the research on the search and identification of QTLs has been carried out on chickens [7]. The chicken QTL database (Chicken QTLdb, https://www.animalgenome.org/cgi-bin/QTLdb/GG/index) contains information on 16656 QTLs of 370 different traits. Most of these QTLs have been identified using both microsatellites [8, 9] and SNPs identified by genotyping of single point mutations [10] or genome-wide analysis [11, 12] as genetic markers.

In contrast to chickens, studies in quails on the identification of QTLs associated with important breeding traits are relatively few in number. To date, the number of such publications is relatively small. A number of works reported on the identification of QTLs using microsatellites, studied the relationship of these genetic markers with growth [13-15], development [16], meat quality [17], and egg productivity [18] indicators. However, it should be noted that when QTL is detected using microsatellites, certain difficulties arise with the identification of the corresponding genes. To solve the problem, the search for SNPs associated with selectively significant traits is carried out, but such studies on quails are limited by the lack of appropriate commercial chips to detect SNPs. In recent years, the number of works on whole genome genotyping has been growing [19]. Using this approach, SNPs were identified and genes associated with productivity indicators [20], behavior [21, 22], plumage color [23, 24], and egg quality [25] in quails were identified.

In this paper, we present the results of genome-wide associative studies of growth rates in F_2 quails of the model resource population in comparison with the dynamics of changes in the body weight of birds aged from 1 day to 8 weeks. The novelty of our approach lies in the creation of a model resource population of quail, which is characterized by a high degree of variability of the studied growth indicators due to the use of maternal and paternal breeds bred in Russia, contrasting in the studied indicators (fast-growing and slow-growing breeds). New SNPs were identified and genes identified with high reliability ($p < 0.00001$) associated with growth rates. The detected SNPs can be further studied as genetic markers in breeding programs to increase the weight of quails, as well as improve other indicators of meat productivity.

The purpose of the work is to identify loci of quantitative traits in the quail genome and analyze the association of the found mutations with live weight, as

well as to characterize allelic variants in F_2 of the obtained model resource population of quails.

Materials and methods. The studies were carried out on the basis of the physiological yard of the Ernst Federal Research Center VIZh in 2021-2022 on 116 females and 116 males of F_2 quails of the model resource population, which were obtained through interbreeding of Japanese and Texas quails. Initially, interbreeding F_1 crossbreeds with bloodlines of 50% Japanese quail and 50% Texas quail were obtained, then the F_1 crossbreeds were crossed with each other. The F_2 progeny was used as a model resource population for molecular genetic studies and assessment of growth dynamics.

Parental quails (original breeds, F_1) were kept in separated multitiered quail cages, at least 250 cm^2 per bird, in groups of 5-6 birds (1 male, 4-5 females) to produce offspring. F_2 quails of the model resource population were kept in multitiered quail cages (no more than 25 birds per tier, stocking density of at least 162 cm^2 per bird). All cages were equipped with a nipple drinker system (at the rate of 1 nipple per 10 birds), mounted feeders (feeding front of at least 3 cm per bitd) and a manure removal system, in connection with which the birds had free access to clean water and a full-scale commercial compound feed. For young quails aged from 1 day to 6 weeks, a compound feed with a nutritional value of 11.92 (2850) MJ/kg (Kcal/kg) and a crude protein content of 285.00 g/kg was used. From the age of 7 weeks, quails were fed with transferred to feed for productive quails with an exchange energy of 12.13 (2900) MJ/kg (Kcal/kg) and a crude protein content of 180.00 g/kg. The temperature in the premice where the birds were kept was maintained at 18 to 25 °C. In brooders, where young animals were kept from hatching to the age of 4 weeks, the temperature varied from 35 to 23 °C as the individuals matured. Humidity in the premice did not exceed 70%.

The quails in the F_2 model resource population ($n = 232$) was weighed (an OHAUS Pioneer PA413C scale, OHAUS, USA) at the age of 1 day, 2, 4, 6, and 8 weeks.

DNA was isolated from tissue samples and quail feather pulp using the DNA-Extran 2 kit (OOO NPF Sintol, Russia) according to the protocol recommended by the manufacturer. The concentration of the obtained DNA was determined on a Qubit 2.0 fluorimeter (Invitrogen/Life Technologies, USA), the purity was assessed spectrophotometrically (NanoDrop 8000, Thermo Fisher Scientific, USA) (DNA with an $OD_{260/280}$ ratio of at least 1.8 was used for subsequent analysis), DNA quality also by gel electrophoresis in 1% agarose gel.

Whole genome genotyping of F_2 quail model resource population was performed using the genotype by sequencing (GBS) method [26]. The matrix was obtained that contained genomic DNA sequences of 232 F_2 individuals. Adapters were removed and the fastq file was demultiplexed (separation by sample; the cutadapt program, version 3.4, https://pypi.org/project/cutadapt/). Quality control of fastq files was performed (fastqc program; version 0.9.11, https://github.com/s-andrews/FastQC). For alignment, the reference genome was used (the bowtie2 package, version 2.4.4, https://github.com/BenLangmead/bowtie2). Variant invocation (SNP) and annotation were carried out (the bcftools package, version 1.13, https://samtools.gith-ub.io/bcftools/bcftools.html). The converted data were loaded into the R package [27] for further calculations. The genome of Japanese quail (Coturnix japonica 2.1, GCF_001577835.2) was used as a reference. From 115906 SNPs, after quality control and filtering of genotyping data (the PLINK 1.9 software package; http://zzz.bwh.harvard.edu/plink/), 92686 SNPs were selected for

GWAS (whole-genome associated study) analysis. SNPs were selected based on the quality of genotyping for all SNPs for each individual not lower than 90%, the frequency of occurrence of minor alleles, and the deviation of the frequency of SNP genotypes from the Hardy-Weinberg distribution in the aggregate of tested samples with a p-value $< 10^{-5}$.

Principal component analysis (PCA, https://www.datacamp.com/tutorial/pca-analysis-r) was performed and visualized (the R ggplot2 package, https://github.com/tidyverse/ggplot2). The data files were prepared in the R4.0 software environment.

Regression analysis using PLINK 1.9 was used to identify associations of SNPs with quail body weight. The reliability of the SNP influence and the identification of significant regions in the quail genome was assessed using the Bonferroni null hypothesis test at a threshold $p < 1\times10^{-5}$. The data were visualized in the qqman package using the R language [27]. The search for candidate genes located in the region of identified SNPs was performed using the Genome assembly Coturnix japonica 2.1 genomic resource (https://www.ncbi.nlm.nih.gov/data-hub/genome/GCF_001577835.2/, accessed 10.07.2022).

Statistical indicators were calculated by multivariate analysis of variance in Microsoft Excel 2013 using arithmetic mean (*M*) and standard error of mean (±SEM), minimum (min), maximum (max), median (*Me*), Pearson's test of agreement ($\chi2$), homozygosity coefficient according to Robertson (Ca), level of polymorphism according to Robertson at 2 alleles (Na).

Results. Obtained F_2 resource population using breeds that are contrasting in genotype and phenotype as the initial parental forms makes it possible to obtain populations of individuals on a relatively small number of birds, characterized by a significantly large range of variability in phenotypic traits. In purebred individuals of the same breed or line, as a rule, the variability decreased due to directed selection for a limited number of traits, which, in the case of using such a bird in molecular genetic studies for the identification of QTL, requires the collection and analysis of phenotypic data on a large sample of individuals. Works on the creation and use of F_2 model resource populations for molecular genetic studies are widely carried out on various types of poultry, e.g., chickens [28], turkeys [29], and quails [19-21]. In quails, lines of the Japanese quail contrasting in the studied trait were mainly used as the initial parental forms [19-21]. In our study, the model resource population derived from interbreeding Japanese and Texas quails. The Japanese quail is an egg breed characterized by a relatively low growth rate, the Texas quail is a meat breed with a high rate of body weight gain.

The body weight of 1-day-old F_2 quails of the model resource ranged from 5 to 11 g and averaged 9±0.1 g. At the age of 2, 4, 6, and 8 weeks, this indicator increased 8-fold, 17-fold, 24-fold, and 28-fold, compared to that for 1-day-old quails (Table 1).

1. Growth dynamics of F_2 the model resource population of quails (Japanese quail × Texas quail) (n = 232, the physiological yard of the Ernst Federal Research Center VIZh, 2021-2022)

Возраст	Body weight, g						
	absolute					gain	
	M	error	max	min	*Me*	absolute	daily
1 сут	9	0.1	11	5	9		
2 нед	69	0.9	117	32	69	61	9
4 нед	157	1.5	214	103	159	88	13
6 нед	219	1.9	322	159	217	62	9
8 нед	252	2.2	354	163	248	33	5

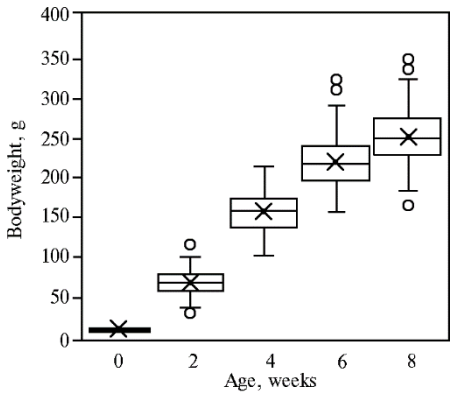

Fig. 1. Bodyweight of quails (Japanese quail × Texas quail) of the F_2 model resource population from 0 to 8 weeks of age (n = 232, the physiological yard of the Ernst Federal Research Center VIZh, 2021-2022).

It should be noted the high variability and significant spread in live weight in birds in the F_2 population. Figure 1 shows a diagram showing the distribution of quails in the study sample according to this indicator in different age periods. It can be seen that the range of variability was 25-40% for the maximum value and 27-54% for the minimum. We revealed the absence of a significant shift in the median in terms of live weight in F_2 quails over the age periods of observation, which indicates a relatively uniform distribution of the frequencies of occurrence of the maximum and minimum values of the trait in the studied population.

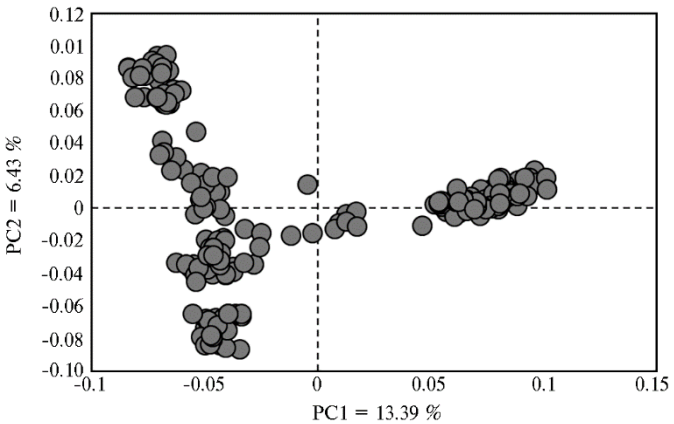

Fig. 2. Genotype by sequencing (GBS)-based PCA analysis of whole genome genotyping data for individuals from the F_2 model resource population of quails (Japanese quail × Texas quail) (n = 232, the physiological yard of the Ernst Federal Research Center VIZh, 2021-2022).

The F_2 heterogeneity of the model resource population of quails in terms of live weight was confirmed by Principal Component Analysis (PCA) based on nucleotide sequence data obtained from individual genome-wide analysis of individuals using the GBS method (Fig. 2). The first component is responsible for 13.39%, the second for 6.43% of genetic differences in birds in the sample under study. According to Figure 2, the studied population was represented by five clusters forming three branches diverging in space from a single point. The heterogeneity of the sample may be due to the structure of the population, consisting of families where there is a greater genetic similarity between individuals belonging to the same group than the average for the population.

To test the assumption about the genomic conditionality of productivity indicators in F_2 quails (in particular, live weight), we conducted a genome-wide association analysis (GWAS). GWAS analysis makes it possible to identify many genomic variants associated with the productive traits of poultry. As a result of the analysis, we identified 149 SNPs with high reliability ($p < 0.00001$) on chromosomes 1, 2, 3, 5, 6, 8, 11, 14, 15, 20, 24, 25, 26, on the chromosomes 1, 2, 3, 5, 11, 26, blocks of 2-9 SNPs related to one gene were detected. The ratio of mutations found in the study with SNPs that are highly associated with body weight,

and SNPs that are characterized by the mechanism of influence, is graphically shown in Figure 3.

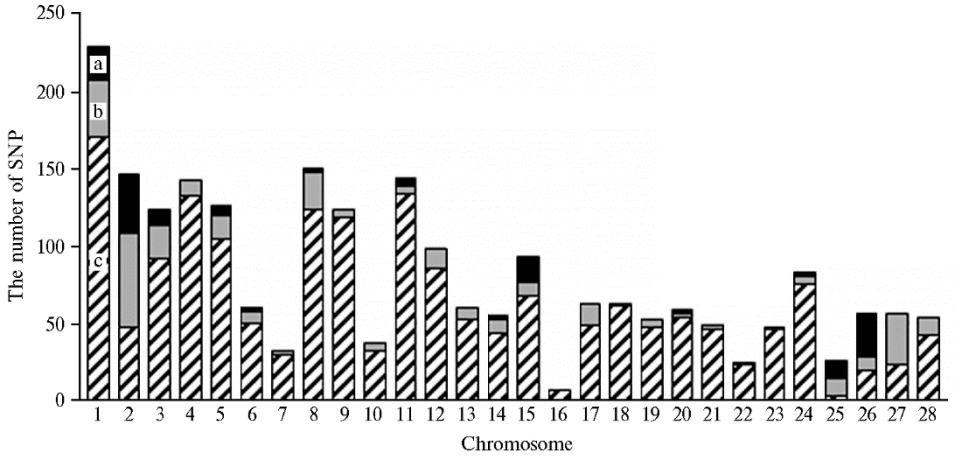

Fig. 3. SNPs associated with bodyweight parameters in quails (Japanese quail × Texas quail) of the F_2 model resource population from 0 to 8 weeks of age: a — characterized SNPs (located near functional genes) with association reliability higher than 1×10^{-5}, b — uncharacterized SNPs (not located near functional genes) with association reliability higher than 1×10^{-5}, c — SNPs with association reliability lower than 1×10^{-5} (n = 232, the physiological yard of the Ernst Federal Research Center VIZh, 2021-2022).

2. SNP and canidate genes associated with bodyweight parameters in 8-week old quails (Japanese quail × Texas quail) of the F_2 model resource population (n = 232, the physiological yard of the Ernst Federal Research Center VIZh, 2021-2022)

Chromosome	The number of SNPs	SNPposition, bp	p	Gene
1	3	142,741,390	7.25×10^{-8}	*PCDH9*
		154,153,381	1.04×10^{-5}	*SMAD9*
		157,425,751	1.35×10^{-5}	*PAN4*
2	2	73,896,881	1.23×10^{-9}	*EGFR*
		7,3896,952	3.67×10^{-8}	
3	1	1,993,165	6.77×10^{-10}	*WDPCP*
5	2	51,581,638	6.71×10^{-5}	*MDGA2*
		51,581,710	6.71×10^{-5}	
1	1	9,015,455	8.51×10^{-5}	*PEPD*

We used SNP loci ($p < 0.00001$) identified in the genome of quails at the age of 8 weeks and associated with the body weight indicator to identify positional and functional candidate genes associated with some mechanism of influence on processes in the body (Table 2). As a result, seven functional candidate genes for chromosomes 1 (*PCDH9*, *SMAD9*, *PAN4*), 2 (*EGFR*), 3 (*WDPCP*), 5 (*MDGA2*) and 11 (*PEPD*).

According to publications, in quails, the *EGFR* gene is responsible for the regulation of granulosa cell proliferation and influences the development of follicles [24]. Other mutations have been reported for other animals and birds as orthologous groups of genes [30], defined bioinformatically using a combination of protein sequence similarity and local synteny data.

We calculated the frequencies of occurrence, the degree of polymorphism, and genetic balance for the identified genes in the studied population of F_2 quails at the age of 8 weeks (Table 3).

According to the results obtained, for all detected point mutations in the genes, there were polymorphic variants of genotypes with a variation in the degree of homozygosity (according to Robertson) from 0.509 to 0.893. Deviations from genetic balance were found for the PAN4 (7.650), EGFR_1 (5.603), EGFR_2 (4.115), and WDPCP (20.819) genes.

3. Frequency of occurance of valuable selectable markers in quails (Japanese quail × Texas quail) of the F_2 model resource population (n = 232, the physiological yard of the Ernst Federal Research Center VIZh, 2021-2022)

Chromosome	Gene	Genotypr frequency, M±SEM			Allele frequency		χ^2	Ca	Na
		11, O and E	12, O and E	22, O and E	1	2			
1	*SMAD9*	0.178±0.019 0.188	0.511±0.024 0.491	0.311±0.022 0.321	0.434	0.566	0.120	0.509	1.966
	PSDH9	0.018±0.006 0.026	0.283±0.021 0.269	0.699±0.022 0.706	0.160	0.840	0.455	0.731	1.367
	PAN4	0.023±0.007 0.075	0.502±0.024 0.398	0.474±0.024 0.526	0.275	0.725	7.650	0.602	1.662
2	*EGFR_1*	0 0.026	0.320±0.021 0.269	0.680±0.022 0.706	0.160	0.840	5.603	0.731	1.367
	EGFR_2	0 0.019	0.274±0.020 0.236	0.726±0.021 0.745	0.137	0.863	4.115	0.764	1.310
3	*WDPCP*	0.065±0.003 0.021	0.159±0.021 0.248	0.776±0.021 0.731	0.145	0.855	20.189	0.752	1.329
5	*MDGA*	0 0.011	0.205±0.019 0.184	0.795±0.019 0.805	0.103	0.897	2.314	0.816	1.226
11	*PEPD_2*	0.009±0.003 0.003	0.095±0.015 0.107	0.896±0.015 0.889	0.057	0.943	2.545	0.893	1.120

N o t e. For the frequency of genotypes and alleles, coding options are given (11 means alleles 1 and 1, 12 means alleles 1 and 2, 22 means alleles 2 and 2); $\chi 2$ — Pearson's goodness-of-fit criterion, Ca — Robertson's homozygosity coefficient, Na — Robertson's polymorphism level at 2 alleles, O and E — observed and expected frequencies, respectively.

An analysis of open information sources showed that to date a small number of works have been published regarding the search and identification of QTLs that are associated with growth rates in quails. M.I. Haqani et al. [19] determined the QTL associated with body weight in quails by examining the age dynamics of this indicator in 277 F_2 individuals derived from crossing lines of Japanese quail with high and normal body weight. Body weight was determined weekly from hatching to 16 weeks of age. As a result, 125 SNPs associated with body weight were identified. On chromosomes 1 and 3, 4 QTLs associated with the body weight of birds aged 4 to 16 weeks were identified. No statistically significant QTLs were found in the early age period (up to 3 weeks) [19)]. S. Vollmar et al. [20] identified QTLs associated with phosphorus, calcium, feed conversion, and body weight gain on 920 F_2 Japanese quails, which were calculated from body weight data at 10 and 15 days of age. A total of 3986 SNPs were selected for analysis. As a result, the authors identified 12 significant SNPs and 4 candidate genes that were associated with the studied traits [20]. J. Recoquillay et al. [21] obtained an F_2 model resource population of Japanese quail by crossing two lines contrasting in behavior. Along with behavioral reactions, productive traits were studied, in particular, body weight at the age of 17 and 65 days and egg production. Based on genome-wide genotyping, 22 QTLs associated with productive traits were revealed. The identified SNPs were found on chromosomes 1, 3, 5, 8, 10, and 18 [21].

In our studies, one of the parental forms during the creation of the resource population was also the Japanese quail. At the same time, the use of Texas quail as a contrast breed made it possible to obtain an F_2 population with a significant range of variability in body weight. The novelty of our study lies in the identification of SNPs and candidate genes that were not previously described in open information sources and are associated with the body weight index in quails during different age periods. Significant SNPs located close to functional genes ($p < 0.00001$) associated with the body weight index of quails aged 8 weeks were localized on 13 of the 28 counted chromosomes, including chromosomes 1, 3, 5 and 8, which is similar to the data obtained by other researchers [19, 21]. The largest number of such SNPs were localized on chromosomes 1, 2, 3, 15, and 27 (see Fig. 3).

Thus, in the obtained F_2 model resource population of quails (Japanese

quail × Texas quail), the genome-wide DNA sequencing revealed 149 SNPs associated ($p < 0.00001$) with body weight on chromosomes 1, 2, 3, 5, 6, 8, 11, 14, 15, 20, 24, 25, and 26. Blocks of 2-9 SNPs linked to one gene were detected on chromosomes 1, 2, 3, 5, 11, and 26. In the regions where the QTLs are located, there are several positional and functional marker candidate genes involved in the determination of traits that are different from the body weight studied in this work. In particular, seven candidate genes (*PCDH9*, *SMAD9*, *PAN4*, *EGFR*, *WDPCP*, *MDGA2*, and *PEPD*) are identified that are significantly ($p < 0.00001$) associated with body weight of quails at 8 weeks age. The data we obtained is the basis for continuing research of the associations of the identified mutations with other selectively significant indicators of productivity.

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