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WHOLE GENOME STUDY OF SINGLE NUCLEOTIDE POLYMORPHISMS' ASSOCIATIONS WITH WITHERS HEIGHT IN LOCAL AND TRANSBOUNDARY BREEDS IN RUSSIA

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Abstract

The stature of an animal is a classic quantitative trait that affects the predisposition to certain diseases and is associated with the productivity of farm animals. Currently, many quantitative trait loci (QTL) have been mapped that affect the cattle's growth constituents, which confirms its polygenic determinism. An assessment of the frequencies of SNPs alleles associated with withers height in cattle populations bred in Russia has been carried out firstly in this work. The prevalence of alleles associated with high stature of animals in three out of four identified single nucleotide polymorphisms in Russian local breeds was revealed. The aim of the work was to identify loci that are under selection pressure and associated with body size in populations of Russian local breeds and transboundary breeds bred in the territory of the Russian Federation, belonging to different types of productivity, as well as with an unequal degree of pressure of artificial selection and distribution in the world. Thirteen cattle breeds ($n = 670$) subjected to our study including Angus ($n = 39$), Ayrshire ($n = 144$), Black-and-White ($n = 50$), Holstein ($n = 184$), Istoben ($n = 22$), Jersey ($n = 32$), Kalmyk ($n = 27$), Kholmogor ($n = 26$), Kyrgyz ($n = 24$), Mongolian ($n = 26$), Tagil ($n = 26$), Yakut ($n = 29$) and Yaroslavl ($n = 41$). Samples of blood, tissue and sperm stored in UNU "Genetic material bank of domestic and wild animal species and birds" of the Ernst Federal Research Center for Animal Husbandry were used as a source of DNA for this study. The samples were genotyped using DNA arrays GGP Bovine 150K and BovineHD BeadChip (Illumina Inc., USA) with the different density. In the course of data processing, SNPs common for the two arrays were determined and were used for further analysis. The genome-wide study of the associations of genotyping data with measurements of physical development of animals was carried out by the PLINK 1.9 program using filters (--geno 0.1), (--mind 0.2), (--maf 0.05). Height at withers for the studied breeds was obtained from the FAO database. All studied breeds were divided into groups according to the following criteria: growth (tall, short), type of productivity (dairy, meat), the degree of pressure of artificial selection (primitive, commercial) and distribution in the world (local, transboundary). Four SNPs were identified in total. Three of them were localized on chromosome 4 (ARS-BFGL-NGS-116590, Hapmap53144-ss46525999, BovineHD0400021479), and one on chromosome 14 (BovineHD1400007259). The alternative alleles in the detected SNPs significantly differ in their frequency in different groups of breeds, and also have significant positive or negative correlations with the height at the withers. The diversity and heterogeneity of the breeds presented in the study allows us to consider the identified traces of selection not as characteristic of one breed, region or type of productivity, but as for a group of breeds of the species *Bos taurus taurus*, the distribution of which from the center of domestication proceeded along the Danube Route. Thus, the identified SNPs can be used as genetic markers in breeding programs in order to increase the stature of animals and their productivity.

Keywords: *Bos taurus*, cattle, local breeds, transboundary breeds, QTL, SNP markers, DNA arrays, GWAS, *PLAG1*, withers' height

Animal breeding aimed at improving the characteristics of cattle is key for sustainable animal husbandry; well-balanced animals are highly productive and are in demand in the livestock market [1].

Whole genome association studies (GWAS) have enabled the identification of many genomic variations associated with the quantitative traits of livestock [2]. Over the past decade, numerous studies have mapped the quantitative trait loci (QTLs) responsible for the dairy yield [3], disease resistance [4, 5], reproductive performance [6], growth [7-9], beef quality [10-13], and carcass weight [14-16] of cattle.

Animal stature is a classic quantitative trait that is of interest to geneticists [17-19]. Apart from providing information on the overall genetic architecture of quantitative traits, a comprehensive understanding of inter-individual growth variability can also elucidate the mechanisms which govern the growth of an organism. Growth influences the predisposition of livestock to certain diseases, and thus, their overall productivity. Although sensitive to environmental factors, humans too are generally influenced by this indicator (~ 85%) [20].

The domestication of cattle was highly influenced by this indicator. The growth of the species *Bos taurus* decreased by approximately 1.5 times from the Neolithic to Middle Ages, and it increased again only in the Early Modern period [21]. The extinct auroch (*Bos primigenius*) was much larger than its domestic descendants (height at the withers ~ 2 m versus ~ 1.1-1.5 m in modern cattle). The heritability coefficient of the indicator varies within 25-85% depending on the population [22, 23]. If the mechanisms of genetic variation have aided the recovery of growth since the Early Modern period, their selection fingerprints should be determined based on the genomic data of modern cattle breeds.

Currently, many QTLs that influence the growth components of cattle have been mapped, which confirms its polygenic determinism. Illustratively, 38 and 52 QTLs have been reported to account for more than 60% of the variation in adult height and weight, respectively, in a population of the American Aberdeen Angus breed [24]. L. Karim et al. [25] examined the Holstein-Friesian and Jersey breeds to identify the QTLs that influence traits responsible for augmenting dairy yield. More than 500 traits were measured, six of which were related to body size: birth weight, weight at 6, 8, 12, 18 and 24 months (body weight), and height at withers at 18 months.

I. Randhawa et al. [26] compared single nucleotide polymorphism (SNP) data across the genome in several European and African breeds of *B. taurus* with high (145-155 cm) and low (105-133 cm) withers, and they found that the most significant selection signal associated with growth is mapped on chromosome 14 (BTA14) within the 24.79-28.25 Mbp region [27]. This selection signature was recently confirmed by full genome sequencing of four *B. taurus* breeds, and it is limited to a smaller region spanning positions within 24.80-25.08 Mbp [28], where the pleomorphic adenoma 1 (*PLAG1*) gene is located.

The *PLAG1* gene, consisting of five exons and four introns, with five transcripts, was first discovered through positional mapping, during the investigation of pleomorphic adenomas of the human salivary glands [29]. *PLAG1* initiates the transcription of insulin-like growth factor 2 (*IGF2*), a mitogenic hormone important for fetal growth and development, and it influences the genetic variability of growth in both humans and cattle [25, 30-32]. Several studies have examined the association of the *PLAG1* gene with various traits, such as calving ease [33], body size [25], birth and yearling weight [14, 35], carcass quality [34] and other traits related to the growth of cattle [36]. However, in Russian local breeds, which are of great interest for biodiversity conservation [37, 38], the role of the *PLAG1*

gene has not been investigated, despite previous genome-wide studies [39, 40].

In this study for the first time the allele frequencies of SNPs associated with withers height in populations of cattle bred in Russia were investigated. In the Russian local breeds, the predominance of alleles associated with high growth of cattle was revealed in 3 out of 4 identified SNPs.

The aim of this study was to identify the loci and characterize allelic variants that are associated with body size, which are under selection pressure in the populations of Russian local breeds and transboundary species bred in the Russian Federation. These breeds have different types of productivity, as well as unequal degrees of artificial selection pressure and global distribution.

Materials and methods. Totally 670 animals of 13 cattle breeds were included in this study: Aberdeen Angus (ANG, $n = 39$), Ayrshire (AYR, $n = 144$), Black and White (BLW, $n = 50$), Holstein (HLS, $n = 184$), Eastoben (IST, $n = 22$), Jersey (JRS, $n = 32$), Kalmyk (KLM, $n = 27$), Kholmogorsk (KHL, $n = 26$), Kyrgyz (KRG, $n = 24$), Mongolian (MNG, $n = 26$), Tagil (TAG, $n = 26$), Yakut (YKT, $n = 29$) and Yaroslavl (YRS, $n = 41$).

The biological material represented whole blood, semen and ear's tissue stored in the Bioresource collection «Bank of genetic materials of domestic and wild animals and birds» of the Ernst Federal Research Center for Animal Husbandry. DNA was isolated using commercial DNA-Extran-1 and DNA-Extran-2 kits (OOO Sintol, Russia) in accordance with the manufacturer's recommendations. The concentrations of dsDNA solutions were determined using a Qubit 3.0 fluorometer (Thermo Fisher Scientific, Wilmington, DE, USA). To check the purity of extracted DNA, OD260/280 ratios were determined using NanoDrop-2000 (Thermo Fisher Scientific, Wilmington, DE, USA).

The genotyping of the samples of 11 breeds was carried out in the Ernst Federal Research Center for Animal Husbandry. The genotypes of two breeds, the Aberdeen Angus and Jersey were downloaded from the publicly available WIDDE database (<http://widde.toulouse.inra.fr/widde/widde/main.do?module=cattle>).

The genotyping of the samples was conducted on SNP chips of different densities, GGP Bovine 150 K and BovineHD BeadChip (Illumina, Inc., USA). During the data processing, SNPs common to the two chips were determined and used for further analysis. Quality control genotyping was performed in PLINK 1.9 [41], using the following filters. At least 90% of loci (--geno 0.1) were successfully genotyped in at least 80% of cattle (--mind 0.2) and the frequency of minor alleles was at least 5% (--maf 0.05). After combining the datasets and quality control of genotyping, 115237 SNPs were included in the analysis.

Employing PLINK 1.9, a GWAS of SNPs associated with withers height was performed. The positions of SNPs were assigned according to the *Bos taurus* genome assembly UMD_3.1.1 (https://www.ncbi.nlm.nih.gov/assembly/GCF_000003055.6).

Withers height data for the studied breeds were obtained from the FAO public database (DAD-IS, <https://www.fao.org/dad-is/data/ru/>, accessed 09/10/2021). Since the values of indicators vary among different countries, the average values were calculated for each breed irrespective of their country and sexuality. Consequently, the average value of the height at withers was calculated for the entire array of the studied breeds. Calculations and visualization of the results were performed using the R software.

Based on the obtained body size data of the cattle, all studied breeds were divided into two groups. Breeds for which the average withers height did not exceed the average values calculated for the entire array were classified as the low group. In contrast, breeds for which the average values of the indicator exceeded the average values of the sample were classified as the high group. Furthermore, the studied breeds were subdivided into groups according to the following criteria:

the type of productivity (dairy, meat), degree of artificial selection pressure (primitive, commercial), and prevalence in the world (local Russian, transboundary).

The significance of the difference in the frequencies of alternative alleles for SNPs that showed significant associations with withers height in different groups of breeds was determined using the χ^2 test in R. The authors excluded Mongolian and Kyrgyz cattle breeds from the analysis because these groups are not bred within Russia in commercial or breeding herds.

Results. The characteristics of the studied cattle breeds are shown in Table 1.

1. Characteristics of the studied Russian local and transboundary breeds of cattle (*Bos taurus taurus*)

Breed	Acronym	Group	Geographic classification (by FAO)	Type of productivity	Degree of artificial selection pressure
Aberdeen Angus	ANG	High	transboundary	meat	commercial
Ayrshire	AYR	High	transboundary	dairy	commercial
Black-and-White	BLW	High	transboundary	dairy	commercial
Kholmogor	KHL	High	local Russian	dairy	commercial
Holstein	HLS	High	transboundary	dairy	commercial
Yaroslavl	YRS	High	local Russian	dairy	commercial
Tagil	TAG	High	local Russian	dairy	commercial
Istoben	IST	High	local Russian	dairy	commercial
Kalmyk	KLM	Low	transboundary	meat	commercial
Jersey	JRS	Low	transboundary	dairy	commercial
Kyrgyz	KRG	Low	–	meat	primitive
Mongolian	MNG	Low	–	meat	primitive
Yakut	YKT	Low	local Russian	meat	primitive

Note. Low and high breeds are designated to cattle for which their average height at withers fall behind and exceed the average values calculated for the entire array, respectively. Dashes mean that the breeds are excluded from the group, since they are not bred in Russia.

Genome-wide association studies using single nucleotide polymorphism markers for withers height (Fig. 1) were conducted for 13 breeds of cattle. Statistically significant (p -value $< 1e-80$) associations were found for some SNPs (Fig. 2).

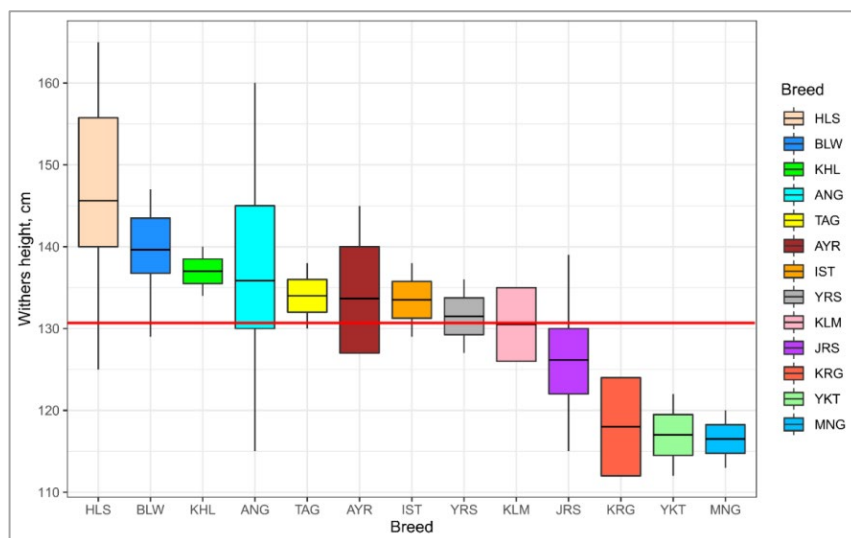


Fig. 1. Average values of the height at the withers for the studied Russian local and transboundary breeds of cattle (*Bos taurus taurus*): HLS — Holstein, BLW — Black-and-White, KHL — Kholmogor, ANG — Aberdeen-Angus, TAG — Tagil, AYR — Ayrshire, IST — Istoben, YRS — Yaroslavl, KLM — Kalmyk, JRS — Jersey, KRG — Kyrgyz cattle, YKT — Yakut, MNG — Mongolian cattle. On the range charts for each breed, the values of the lower quartile, the average value and upper quartile are given. The red line is the average value calculated for the entire array of studied breeds.

In total, four SNPs were identified. Three of these SNPs were located on chromosome 4, and the remaining was located on chromosome 14.

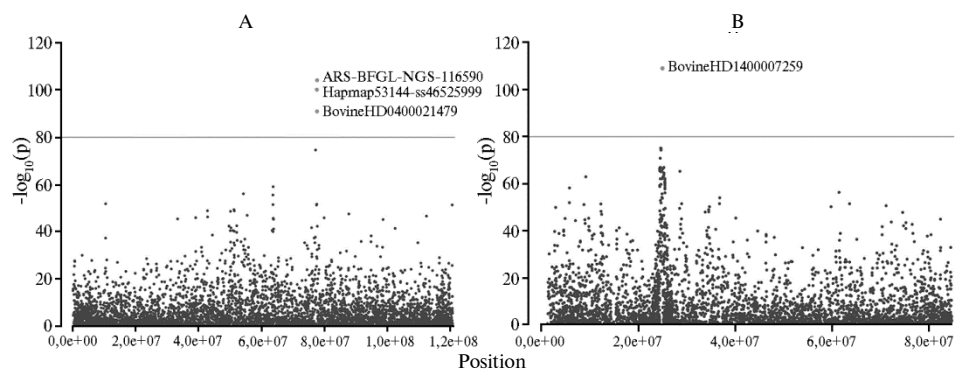


Fig. 2. Localization of single nucleotide polymorphisms significantly associated with height at the withers in Russian local and transboundary breeds of cattle (*Bos taurus taurus*): A — chromosome 4, B — chromosome 14.

We searched for genes located within ± 200 Kb of the detected SNPs (Table 2).

2. Genes found in the region of localization of single nucleotide polymorphisms significantly associated with height at the withers in Russian local and transboundary breeds of cattle (*Bos taurus taurus*)

SNP name	Chromosome	Position	Region, Mb	Genes	Traits
Hapmap53144-ss46525999	4	77555681	77.3-77.8	<i>PURB, MIR4657,</i>	Duration of pregnancy, synthesis of milk components, protein and fat metabolism, average daily weight gain
BovineHD0400021479	4	77613816		<i>H2AFV, PPIA, ZMIZ2, OGDH, TMED4,</i>	
ARS-BFGL-NGS-116590	4	77635835		<i>DDX56, NPC1L1, NUDCD3, CAMK2B, YKT6</i>	
BovineHD1400007259	14	25015640	24.8-25.2	<i>LYN, RPS20, MOS, PLAG1, CHCHD7, SDR16C5, SDR16C6</i>	Growth, constitution, feed intake, fertility

The region 24.8-25.2 Mb located on chromosome 14 contains genes which are associated with body size [42, 43], food intake [44, 45], and fertility [46]. On chromosome 4 within the 77.3-77.8 Mb region, genes associated with metabolism [47], milk composition [48, 49] and milk synthesis [50], and average daily body weight gain [51], were identified. S.M. Ghoreishifar et al. [52] examined breeding patterns in a group of five cattle breeds originating from northern, middle and southern parts of Sweden. The genome regions where the most significant selection signals were found on BTA5 (105.75-106.52), BTA1 (2.25-2.52) and BTA14 (24.42-25.11 and 25.35-25.73). Annotation of genes in these regions made possible to identify both already known and new candidate genes associated with high-altitude hypoxia (*DCAF8, PPP1R12A, SLC16A3, UCP2, UCP3, TIGAR*), cold acclimatization (*AQP3, AQP7, HSPB8*), body size and growth (*PLAG1, KCNA6, NDUFA9, AKAP3, C5H5112orf1, RAD51AP1, FGF6, TIGAR, CCND2, CSMD3*), resistance to diseases and bacterial infections (*CHI3L2, GBP6, PPFIBP1, REP15, CYP4F2, TIGD2, PYURF, SLC10A2, FCHSD2, ARHGEF17, RELT, PRDM2, KDM5B*), reproductive qualities (*PPP1R12A, ZFP36L2, CSPP1*), milk yield and milk composition (*NPC1L1, NUDCD3, ACSS1, FCHSD2*).

Our data correlates with those of previously published papers. Meanwhile, some regions located on other chromosomes and described in the previous studies [53-55] were not identified in our sample. Interestingly, studies conducted by other researchers, including those using contrast breeds, did not reveal the associations of SNPs located in the region of 77.3-77.8 Mb on BTA4 with the withers height [56-58].

The frequencies of alternative alleles for the SNPs detected in each breed

were calculated (Table 3).

3. Allele frequencies at loci significantly associated with height at withers in Russian local and transboundary breeds of cattle (*Bos taurus taurus*)

Breed	Group	Chromosome 4						Chromosome 14	
		ARS-BFGL-NGS-116590		Hapmap53144-ss46525999		BovineHD0400021479		BovineHD1400007259	
		<i>T</i>	<i>G^a</i>	<i>T^a</i>	<i>C</i>	<i>A</i>	<i>G^a</i>	<i>T</i>	<i>G^a</i>
HLS	High	0.82	99.18	99.18	0.82	0.82	99.18	0.54	99.46
BLW	High	1.00	99.00	99.00	1.00	1.00	99.00	0.00	100.00
KHL	High	23.08	76.92	76.92	23.08	23.08	76.92	13.46	86.54
ANG	High	62.82	37.18	36.84	63.16	62.82	37.18	0.00	100.00
TAG	High	26.92	73.08	73.08	26.92	26.92	73.08	9.62	90.38
AYR	High	28.47	71.53	71.53	28.47	28.47	71.53	21.88	78.13
IST	High	45.00	55.00	54.55	45.45	36.36	63.64	9.52	90.48
YRS	High	45.12	54.88	55.00	45.00	45.12	54.88	17.50	82.50
KLM	Low	95.83	4.17	3.85	96.15	96.15	3.85	94.23	5.77
JRS	Low	95.31	4.69	4.69	95.31	95.31	4.69	100.00	0.00
KRG	Low	72.92	27.08	29.17	70.83	52.27	47.73	85.42	14.58
YKT	Low	98.28	1.72	0.00	100.00	87.50	12.50	98.28	1.72
MNG	Low	100.00	0.00	6.25	93.75	89.58	10.42	100.00	0.00

Note. HLS — Holstein, BLW — Black and White, KHL — Kholmogor, ANG — Aberdeen Angus, TAG — Tagil, AYR — Ayrshire, IST — Istoben, YRS — Yaroslavl, KLM — Kalmyk, JRS — Jersey, KRG — Kyrgyz cattle, YKT — Yakut, MNG — Mongolian cattle; Low — breeds that have the average height at the withers did not exceed the average values calculated for the entire array; High — breeds that have the average height at the withers exceeded the average values of the sample: ^a — alleles associated with high stature in cattle.

The most significant differences between the frequencies of alternative alleles were observed in the low-breed group. Illustratively, in the ARS-BFGL-NGS-116590 locus, the frequencies of G/T alleles varied from 0 to 27.08% and from 72.92 to 100%, respectively; at the Hapmap53144-ss46525999 locus, T/C allele frequencies ranged from 0 to 29.17% and from 70.83 to 100%; at the BovineHD1400007259 locus, the G/T allele frequencies ranged from 0 to 14.58% and from 85.42 to 100%. While in the high-breed group, the most significant difference in the frequencies of T/G alleles (0 and 100%, respectively) was observed in the BovineHD1400007259 locus in Black-and-White and Aberdeen Angus breeds.

One of the alternative alleles was absent in some breeds; therefore, the differences between the frequencies of alternative alleles were not assessed for each breed separately, but for all the groups formed according to different traits (Table 4).

4. The differences between the frequencies of alternative alleles at the loci associated with the withers height in the different groups of Russian local and transboundary cattle breeds (*Bos taurus taurus*)

Group	Chromosome 4						Chromosome 14					
	ARS-BFGL-NGS-116590			Hapmap53144-ss46525999			BovineHD0400021479			BovineHD1400007259		
	<i>T</i>	<i>G^a</i>	<i>p</i>	<i>T^a</i>	<i>C</i>	<i>p</i>	<i>A</i>	<i>G^a</i>	<i>p</i>	<i>T</i>	<i>G^a</i>	<i>p</i>
High	0.204	0.796	***	0.795	0.205	***	0.201	0.799	***	0.09	0.91	***
Low	0.349	0.651	***	0.082	0.918	**	0.309	0.647	***	0.959	0.041	ns
Meat	0.839	0.161	ns	0.168	0.832	ns	0.77	0.230	ns	0.687	0.313	***
Milk	0.218	0.782	***	0.781	0.219	***	0.215	0.785	***	0.152	0.848	***
Commercial	0.276	0.724	***	0.721	0.279	***	0.275	0.725	***	0.177	0.823	***
Primitive	0.909	0.091	***	0.112	0.888	***	0.777	0.223	***	0.948	0.052	ns
Transboundary	0.256	0.744	***	0.740	0.260	***	0.259	0.741	***	0.187	0.813	***
Local Russian	0.486	0.514	*	0.514	0.486	*	0.448	0.552	ns	0.306	0.694	***

Note. ^a — alleles associated with high stature in cattle.

* *p* < 0.05, ** *p* < 0.01; *** *p* < 0.001, ns — not significant.

Generally, the frequencies of alternative alleles in the studied groups were significantly different. The exception was the group of beef cattle in all three SNPs found on BTA4. In addition, the frequencies of the SNP BovineHD1400007259 did not differ from those theoretically expected from the primitive cattle. A similar situation was observed in the undersized cattle group. This may be attributed to

the fact that three out of their five breeds belong to primitive cattle (Kyrgyz and Mongolian cattle, Yakut breed).

In the Aberdeen Angus breed, similar trends in the distribution of allele frequencies on chromosome 4 were observed as that of the low-breed group, even though they belong to the high-breed group.

The G allele at the BovineHD0400021479 locus, the G allele at the ARS-BFGL-NGS-116590 locus, the G allele at the BovineHD1400007259 locus, and the T allele at the Hapmap53144-ss46525999 locus are associated with large height at the withers. For the SNP BovineHD1400007259, located within the PLAG1 gene, the G allele frequencies associated with high stature correlated with those from the previous studies on Holstein-Friesian and Jersey breeds [25]. Previously, Hou J. et al. [58] studied the association of SNP rs109815800 (AC_000171.1:g.25015640, G > T, designated on the chip as BovineHD1400007259) in the PLAG1 gene with cattle growth. The results of the association analysis showed that cattle breeds with the T/T genotype were shorter than those with T/G or G/G genotypes ($p < 0.001$).

A statistically significant correlation was determined between the frequencies of alternative alleles and withers height for all detected SNPs (Table 5).

5. Correlation between the withers height and the frequency of alternative alleles in the loci associated with the height at the withers in different groups of Russian local and transboundary cattle breeds (*Bos taurus taurus*)

Group	Chromosome 4						Chromosome 14	
	ARS-BFGL-NGS-116590		Hapmap53144-ss46525999		BovineHD0400021479		BovineHD1400007259	
	<i>T/G</i> ^a	<i>p</i>	<i>T^a/C</i>	<i>p</i>	<i>A/G</i> ^a	<i>p</i>	<i>T/G</i> ^a	<i>p</i>
High	0.722	***	0.719	***	0.708	***	0.678	***
Low	-0.172	ns	-0.281	ns	-0.498	**	-0.063	ns
Meat	0.530	***	0.456	*	0.090	ns	0.767	***
Milk	0.908	***	0.908	***	0.907	***	0.751	***
Commercial	0.829	***	0.827	***	0.821	***	0.729	***
Primitive	0.962	***	0.859	***	0.96	***	0.975	***
Transboundary	0.876	***	0.875	***	0.876	***	0.84	***
Local Russian	0.981	***	0.982	***	0.989	***	0.971	***
All samples	0.838	***	0.826	***	0.752	**	0.854	***

Note. ^a — alleles associated with high stature in cattle. Correlation coefficients are shown for the "high" allele.

* $p < 0.05$, ** $p < 0.01$; *** $p < 0.001$, ns — not significant.

Significant correlations were found between high allele frequencies and the withers height in almost all breed groups. Interestingly, for the low-breed group, contrary to the expectation, no significant negative correlation was found at the BovineHD1400007259 locus.

Thus, we identified that SNPs ARS-BFGL-NGS-116590, Hapmap53144-ss46525999, BovineHD0400021479, and BovineHD1400007259, localized, according to the assembly of the *Bos taurus* UMD 3.1.1 genome, on chromosomes 4 and 14, were associated with cattle withers height. The frequencies of the identified SNPs among breeds differed significantly from that of a randomly possible outcome. Alternative alleles in the detected SNPs were determined, and they had statistically significant positive or negative correlations with withers height. Thus, it can be inferred that the selection pressure on these loci is not the same for different breeds. The diversity and heterogeneity of the breeds shown by the sample allows us to consider that the identified traces of selection aren't the characteristic of one breed, region, or productivity type, but are the characteristic for a group of breeds of the species *Bos taurus taurus* that migrated from the center of domestication along the Danube route. Thus, the identified SNPs can be used as genetic markers in breeding programs to improve cattle stature and their overall productivity.

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