Article

Genome-Wide Screening for SNPs Associated with Stature in Diverse Cattle Breeds [†]

Alexandra S. Abdelmanova [1,*], Alexander A. Sermyagin [1], Arsen V. Dotsev [1], Nikolay V. Bardukov [1], Margaret S. Fornara [1], Gottfried Brem [1,2] and Natalia A. Zinovieva [1]

1   L.K. Ernst Federal Research Center for Animal Husbandry, Dubrovitsy, Podolsk Municipal District, 142132 Podolsk, Moscow Region, Russia
2   Institute of Animal Breeding and Genetics, University of Veterinary Medicine (VMU), Veterinärplatz, A-1210 Vienna, Austria
*   Correspondence: preevetic@mail.ru
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Abstract: Cattle breeds used in industrial production tend to be larger than local cattle, as increased dairy and beef productivity is closely related to stature. This study aimed to identify single nucleotide polymorphisms (SNPs) significantly associated with stature in diverse cattle breeds. Thirteen local and transboundary cattle breeds ($n = 670$) were divided into two groups according to their stature. The high-stature group included the Angus, Ayrshire, Black-and-White, Holstein, Kholmogor, Yaroslavl, Tagil, and Istoben breeds. The low-stature group included Jersey, Kalmyk, Kyrgyz, Mongolian, and Yakut. The average height at withers was 136.3 ± 1.6 and 121.6 ± 2.8 cm in the high- and low-stature groups, respectively. The samples of the 11 breeds were genotyped using high-density DNA arrays. Genotypes of the two remaining breeds were downloaded from the publicly available WIDDE database. Genome-wide association studies revealed seven SNPs strongly associated with stature, including three at 77.3–77.8 cM on BTA4 and four at 24.5–25.2 cM on BTA14. Functional annotation showed the localization within identified regions of genes responsible for growth, exterior characteristics, protein and lipid metabolism, and feed intake. The identified SNPs can be considered useful DNA markers for marker-assisted cattle breeding aimed at increasing stature.

Keywords: local cattle; GWAS; SNP; QTL; stature; allele frequency

1. Introduction

Body size, an archetypical quantitative or complex trait that exhibits continuous variation [1], has been extensively studied because it is ecologically important, relevant in farming, and an important indicator of growth and health [2]. Stature and body weight in beef cattle breeding are important for beef production. In dairy farming, smaller or larger animals may be desirable, depending on management considerations [3,4].

Many studies have revealed a large number of quantitative trait loci (QTLs) associated with body size in cattle [5,6]. QTLs that affect the growth components of cattle have been mapped, confirming their polygenic determinism [7,8]. For example, 38 and 52 QTLs have been reported to account for more than 60% of the variation in adult height and weight, respectively, in the American Aberdeen Angus cow population [9].

A QTL on chromosome 14 with a major effect on stature and body weight was reported by Karim et al. [10] in Holstein Friesian and Jersey animals, as well as by others in many other independent populations [11–14]. Randhawa et al. [15] compared SNP data across the genome in a number of European and African breeds of *Bos taurus* with high (145–155 cM) and low (105–133 cM) withers and found the most significant selection signal associated with growth to be mapped on chromosome 14 (BTA14) in the 24.79–28.25 Mb region [16]. A detailed analysis of the fine mapping of this chromosome 14 locus [10]

yielded 13 candidate polymorphisms potentially underlying the QTL. Further functional and genetic analyses reduced the number of candidate variants to two polymorphisms in the bidirectional promoters of the *PLAG1* and *CHCHD7* genes. In particular, *PLAG1* is an obvious candidate, given *PLAG1* knockout mice suffer from slow growth rates and dwarfism [17,18]. This gene encodes a transcription factor that regulates several growth factors including *IGF2* [19,20], a key modulator of growth in both dogs and humans [21,22]. However, most studies were conducted on commercial cattle breeds subjected to strong artificial selection pressures [15,23,24].

Although comprehensive genome-wide studies of local Russian cattle breeds have been carried out [25–27], the genetic basis of stature in these breeds has not been investigated. Despite local breeds having lower productivity compared to that of commercial breeds, their adaptability to climate conditions makes them useful as reserves of genetic diversity in breeding programs.

This study aimed to identify SNPs significantly associated with stature in commercial and local cattle of different productivity types bred in Russia and nearby countries.

2. Materials and Methods

Totally 670 samples of thirteen local and transboundary cattle breeds, including Aberdeen-Angus (ANG, *n* = 39), Ayrshire (AYR, *n* = 144), Black-and-White (BLW, *n* = 50), Holstein (HLS, *n* = 184), Istoben (IST, *n* = 22), Jersey (JRS, *n* = 32), Kalmyk (KLM, *n* = 27), Kholmogor (KHL, *n* = 26), Kyrgyz (KRG, *n* = 24), Mongolian (MNG, *n* = 26), Tagil (TAG, *n* = 26), Yakut (YKT, *n* = 29) and Yaroslavl (YRS, *n* = 41), were subjected to our study.

The samples of 11 breeds stored in the bioresource collection "Bank of genetic materials of domestic and wild animals and birds" of the L.K. Ernst Federal Research Center for Animal Husbandry were genotyped using high-density DNA arrays (Illumina Inc., San Diego, CA, USA). The genotypes of the two remaining breeds, Aberdeen–Angus and Jersey, were downloaded from the WIDDE database [http://widde.toulouse.inra.fr/wide].

Since genotyping of the samples was carried out on SNP chips of different densities, Bovine GGP HD Bead Chip and BovineHD BeadChip (Illumina, Inc., San Diego, CA, USA), which included of ~150 K and 777 K SNPs, respectively, during data processing. SNPs common to the two chips were determined and used for further analysis. Quality control of genotyping was carried out in PLINK 1.9 [28] using the following filters: at least 90% of loci (—geno 0.1) were successfully genotyped in at least 80% of animals (—mind 0.2) and the frequency of minor alleles was at least 5% (–maf 0.05). After combining the data sets and quality control of genotyping, 115,237 SNPs were used for the subsequent genome-wide association studies (GWAS).

We compared the genome-wide genotypes of 532 animals representing eight high-stature breeds and 138 animals of five low-stature breeds. To identify SNPs that were significantly associated with withers height and body weight we carried out across-breed GWAS using PLINK 1.9. A linear regression using a linear-mixed model was applied, and defined as follows:

$$y = Xb + Wg + e,$$

where *y*—a vector of phenotype traits; *b*—a vector of fixed effects including breed, and linear discriminant functions; *g*—a vector for the SNP effects; *e*—a vector of random residual effects with $e \sim N(0, I\sigma^2 e)$; and *X, W*—incidence matrices for *b* and *g*, respectively. To confirm the significant impact of SNPs and identify significant regions in the genome of cattle, several tests were used to check for null hypotheses by Bonferroni (threshold $p < 4.34 \times 10^{-7}$, 0.05/115,237).

The positions of the SNPs were assigned according to the *Bos taurus* genome assembly UMD 3.1.1 (https://www.ncbi.nlm.nih.gov/assembly/GCF_000003055.6, accessed on 1 October 2021).

The Domestic Animal Diversity Information System (DAD-IS) (http://www.fao.org/dad-is/en, accessed on 1 October 2021) maintained and developed by the Food and Agriculture Organization (FAO) was used to obtain the information concerning withers height and

weight for the studied breeds. Since the values of the indicators varied in different countries, the average values were calculated for each breed without considering the country of breeding and the sex of the animal.

3. Results

The cattle breeds were divided into two groups according to their stature [29]. The breeds that have their average stature above the overall average stature were categorized into the high-stature group. Other breeds were assigned to the low-stature group. The high-stature group included the Angus, Ayrshire, Black-and-White, Holstein, Kholmogor, Yaroslavl, Tagil, and Istoben breeds. The low-stature group comprised of Jersey, Kalmyk, Kyrgyz, Mongolian, and Yakut cattle. The average values for height at withers and weight in the high-stature and low-stature groups were 136.3 ± 1.6 and 121.6 ± 2.8 cm and 697.8 ± 22.8 and 457.3 ± 41.5 kg, respectively (Figure 1).
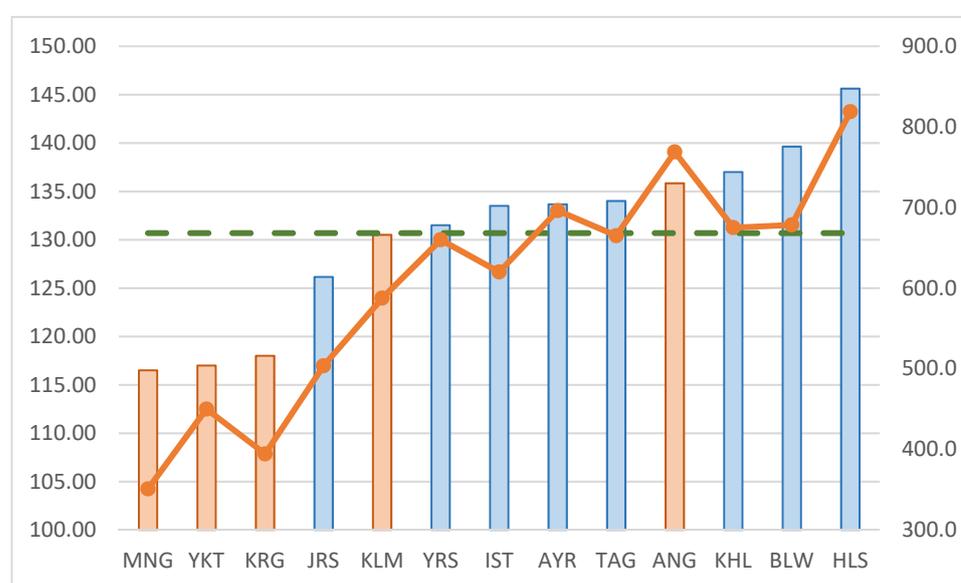
Figure 1. Distribution of height at withers and body weight in the studied breeds. Height at withers shown by colored bars in centimeters (left axis) and body weight shown by an orange line in kilograms (right axis). Breeds of different productivity types shown by blue (dairy type) and red (beef type) bars. Green dashed line indicates the overall average value of height at withers. The breeds' abbreviations are explained in the Materials and Methods section.

Genome-wide association studies (Figure 2) revealed seven SNPs strongly associated with stature: three at 24.5–25.0 cm on BTA14 were associated with body weight only (BovineHD1400007132, $p < 4.264 \times 10^{-81}$; BovineHD1400007161, $p < 1.529 \times 10^{-88}$; BovineHD1400007247, $p < 6.145 \times 10^{-82}$); one at BTA4:77613816 with height at withers only (BovineHD0400021479; $p < 1.173 \times 10^{-91}$); and three at 77.3–77.8 cm on BTA4 (Hapmap53144-ss46525999, $p < 7.747 \times 10^{-101}$ for height and $p < 4.865 \times 10^{-83}$ for weight; ARS-BFGL-NGS-116590, $p < 7.665 \times 10^{-105}$ for height and $p < 6.098 \times 10^{-87}$ for weight) and at 25.2 cM on BTA14 (BovineHD1400007259, $p < 1.324 \times 10^{-109}$ for height and $p < 4.3 \times 10^{-126}$) were associated with both.

The allele frequencies of the significantly associated SNPs separately for each breed (Supplementary Table S1) and average values in the two groups were calculated (Table 1).
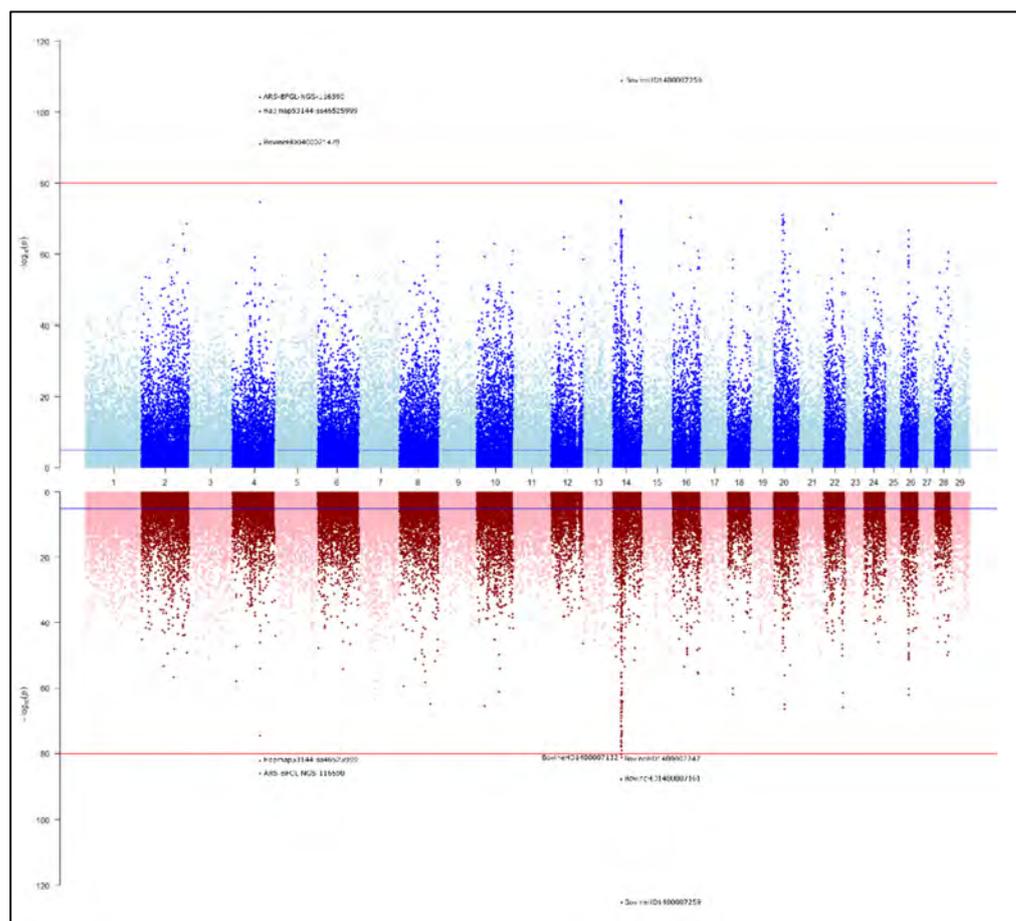
Figure 2. Genome-wide association studies for the height at withers (upper panel) and body weight (lower panel) for the studied breeds. The lines represent the significant thresholds by Bonferroni correction (blue line, $-\log_{10}(p) > 7$) and the most significant SNPs (red line, $-\log_{10}(p) > 80$).

Table 1. Frequencies of alternative alleles at the loci associated with the height at withers and body weight in different groups of cattle breeds.

Localization	Trait	SNP	Allele	Allele Frequencies	
				High-Stature Breeds	**Low-Stature Breeds**
Chr 4	Height	BovineHD0400021479	T	0.28	0.84
			C [a]	0.72	0.16
	Height and Weight	ARS-BFGL-NGS-116590	T	0.29	0.92
			G [a,b]	0.71	0.08
		Hapmap53144-ss46525999	A [a,b]	0.71	0.09
			G	0.29	0.91
Chr 14	Weight	BovineHD1400007259	G [a,b]	0.91	0.04
			T	0.09	0.96
		BovineHD1400007247	A [b]	0.95	0.45
			G	0.05	0.55
		BovineHD1400007132	A [b]	0.93	0.36
			G	0.07	0.64
		BovineHD1400007161	T [b]	0.84	0.14
			G	0.16	0.86

[a]—alleles associated with greater height at withers. [b]—alleles associated with greater body weight.

The differences between the average frequencies of alternative alleles in the high–stature group were observed for SNPs located on BTA14: 24.5–25.2. The frequencies varied from 0.05/0.95 for G/A alleles in the BovineHD1400007247 to 0.16/0.84 for G/T alleles in the BovineHD1400007161. In the low-stature group, the alleles' frequencies essentially differ for SNPs located in BTA4: 77.3–77.8. The frequencies varied from 0.08/0.92 for G/T alleles in the ARS-BFGL-NGS-116590 to 0.16/0.84 for G/T alleles in the BovineHD0400021479. The most differences between the frequencies of alternative alleles were observed for SNP BovineHD1400007259 located on BTA14 for both groups of the breeds.

A significant correlation was found between the frequencies of alternative alleles and the studied traits (height at withers and body weight) for all detected SNPs (Table 2).

Table 2. Correlation coefficients of alleles' frequencies with the height at withers and body weight.

Localization	SNP	Alleles	High-Stature Breeds		Low-Stature Breeds	
			Height	Weight	Height	Weight
Chr 4	BovineHD0400021479	T/C [a]	0.708 **		−0.498 ns	
	ARS-BFGL-NGS-116590	T/G [a]	0.722 **	0.216 ns	−0.172 ns	−0.233 ns
	Hapmap53144-ss46525999	A [a,b]/G	0.719 **	0.216 ns	−0.281 ns	−0.413 ns
Chr 14	BovineHD1400007259	G [a,b]/T	0.678 **	0.527 ns	−0.063 ns	−0.079 ns
	BovineHD1400007247	A [b]/G		0.650 *		−0.062 ns
	BovineHD1400007132	A [b]/G		0.584 *		−0.170 ns
	BovineHD1400007161	T [b]/G		0.750 **		−0.338 ns

[a]—alleles associated with greater height at withers. [b]—alleles associated with greater body weight. * $p < 0.05$; ** $p < 0.01$; ns–not significant.

Strong and moderate correlations were observed only in the high-stature breed group. In the low-stature breed group, there was no correlation between the stature and allele frequencies (Supplementary Table S2).

A search for genes located within ±200 kb of the detected SNPs identified genes *PURB*, *MIR4657*, *H2AFV*, *PPIA*, *ZMIZ2*, *OGDH*, *TMED4*, *DDX56*, *NPC1L1*, *NUDCD3*, *CAMK2B*, and *YKT6*, associated with metabolism [30], composition of milk [31,32], synthesis of milk fat and protein [33], and average daily body weight gain [34] in the region BTA4: 77.3–77.8 Mb.

4. Discussion

Our results agree with the previous studies, indicating that the 24.8–25.2 Mb region on BTA 14 containing the *PLAG1* gene is strongly related to body size. Previous studies were conducted on well-selected European or American breeds of dairy (Holstein and Jersey [10], Montbeliarde [35], Swedish Holstein–Friesian and Swedish Red Cattle [36]) and beef types (Gelbvieh beef cattle [37], Simmental, Brahman [38]) or both types of breeds (multibreed cohorts [5]).

Studies on some Asian local breeds (Hanwoo and Japanese Black cattle) found significant associations of *PLAG1* gene with the carcass weight [39,40], but not in the Wagyu population [40]. At the same time, two downstream regions (BTA14: 46.5–46.9 Mb and 60.2–60.5 Mb) containing *FABP5* and *OXR1* genes, respectively, were identified and showed significant association with chuck roll weight and bicep weight for Wagyu, but not for Chinese Simmentals [41]. In contrast, Rowan et al. [42] showed associations of carcass merit with the region containing the *OXR1* gene for Red Angus and Simmental cattle.

In addition, recent studies have revealed that the region on BTA14: 26–27 Mb was associated with the traits of primal cut yields [43], indicating that a wide region on chromosome 14 was associated with the growth and development of the organism. This was common for different groups of breeds irrespective of origin, productivity type, and the intensity of selection in the population.

However, the regions described in previous studies and located on other chromosomes [14,44,45] were not identified in our sample. In addition, we identified the 77.3–77.8 Mb region on BTA 4, which was not shown to be associated with height at withers in previous studies including those using contrast breeds [15,46–48].

Structural and functional annotation revealed the presence of genes associated with metabolism, milk composition, and synthesis, as well as average daily gain.

Alternative allele frequencies were significantly different in the high- and low-stature breeds for SNPs associated with the height at withers.

No significant difference was found in the frequencies of SNPs associated with body weight on comparing the high- and low-stature cattle groups. However, beef and dairy breeds showed significant differences in allele frequencies of these SNPs (Supplementary Table S2), because the group of low-stature breeds consisted mainly of representatives of primitive breeds (Mongolian, Yakut, and Kyrgyz) in which, until recently, selection work has not been carried out. Almost all low-stature breeds (except Jersey) exhibit beef-type productivity. These have been bred for centuries by nomadic tribes in the harsh climate of the steppes and semi-deserts of Central Asia, survive under poor forage conditions in short dry summers and cold winters, and can be quickly fattened with improved feeding [49]. They were not selected to increase height, but for beef production.

The group of high-stature cattle is represented mainly by dairy breeds, which for a long time have been subjected to strong selection pressure, including increased growth.

Despite the Aberdeen Angus breed being assigned to the high-stature breed group, the same trends were observed in the distribution of allele frequencies in the SNPs located on chromosome 4 associated with height and height/weight traits in the low-stature breed group. This corresponds to the existing exterior and purpose of the breed: the animals are not high relative to specialized dairy (for example, Holstein) breeds; they have a lot of weight because of their better ability to fatten and accumulate subcutaneous fat [50]. Animals of primitive breeds (Mongolian, Yakut, and Kyrgyz) mainly formed the low-stature and beef groups.

5. Conclusions

Using across-breed genome-wide association studies, we were able to identify the SNPs, which are significantly associated with stature and body weight. The SNPs located at BTA4: 77.3–77.8 Mb were associated with the withers height (BovineHD0400021479) and withers height/body weight traits (ARS-BFGL-NGS-116590, Hapmap53144-ss46525999) for groups of high-stature and low-stature breeds and dairy-type breeds, but not for beef-type breeds. For beef-type breeds, significant differences in alleles' frequencies of above-mentioned SNPs were observed only for body weight.

The alleles' frequencies of SNPs on BTA14: 24.5–25.2 Mb associated with both the withers height/body weight (BovineHD1400007259) and body weight (BovineHD1400007247, BovineHD1400007132 and BovineHD1400007161) were significantly different in the group of intensively selected dairy breeds.

The identified SNPs can be considered useful DNA markers for marker-assisted cattle breeding to increase withers height in intensively selected commercial breeds, but not in local and primitive cattle. Additional research is required to reveal the genetic mechanisms of stature formation in primitive breeds.

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