

Association of SNP in the *KAT6B* gene with live weight of heifers of the Yaroslavl cattle breed

Igoshin A.V.¹, Yudin N.S.^{1, 2}, Ilina A.V.³, Larkin D.M.^{4*}

¹ Institute of Cytology and Genetics, SB RAS, Novosibirsk, Russia

² Kurchatov Genomic Center of the Institute of Cytology and Genetics, SB RAS, Novosibirsk, Russia

³ Federal Williams Research Center for Forage Production and Agroecology, Scientific Research Institute of Livestock Breeding and Forage Production, Yaroslavl Region, Russia

⁴ Royal Veterinary College, University of London, London, United Kingdom

* dmlarkin@gmail.com

Key words: cow; Yaroslavl breed; weight; withers height; *MSS51* gene; *KAT6B* gene; single nucleotide polymorphism; association

Motivation and Aim: Previously, using the whole genome genotyping, we showed that the Yaroslavl breed has unique genetics compared to other Russian and foreign cattle breeds, while foreign breeds had an insignificant impact on the gene pool of Yaroslavl cattle [1]. Analysis of whole genome sequencing data of the Yaroslavl cows and data from the “1000 Bull Genomes” project made it possible to identify a unique haplotype on chromosome 28, which is found almost exclusively in Yaroslavl cattle breed [2]. This haplotype contains the *KAT6B* gene and appears to be negatively associated with withers height, heart girth and live weight at different ages. So probably, it has undergone purifying selection in other cattle breeds.

Methods and Algorithms: DNA fragment containing the missense variant G>A (p.Val105Met) within the *KAT6B* gene was amplified by PCR. The amplicons were cut with *HpySE526 I* restriction enzyme (SibEnzyme Ltd). The association between phenotypes obtained from individual heifer record cards and genotypes was estimated using linear regression (‘lm’ R function).

Results: We genotyped an additional 112 heifers to study the negative association of the Val105Met mutation in the *KAT6B* gene with live weight in Yaroslavl cows. The association we found earlier was confirmed in a pooled sample of 142 animals (Table 1, Fig. 1).

Table 1. Associations of Val105Met mutation in the *KAT6B* gene with weight of heifers of the Yaroslavl cattle breed at different ages. LM is a linear model, LM-PCs is a linear principal component-corrected model, and β is the effect size (kg/allele)

Weight	LM		LM-PCs	
	β	<i>p</i>	β	<i>p</i>
At birth	−0.28	0.5828	−0.27	0.5732
6 months	−6.76	0.0036	−6.25	0.0054
10 months	−5.68	0.0667	−5.77	0.0334
12 months	−8.36	0.0219	−8.2	0.0103
18 months	−12.62	0.0078	−11.25	0.0093

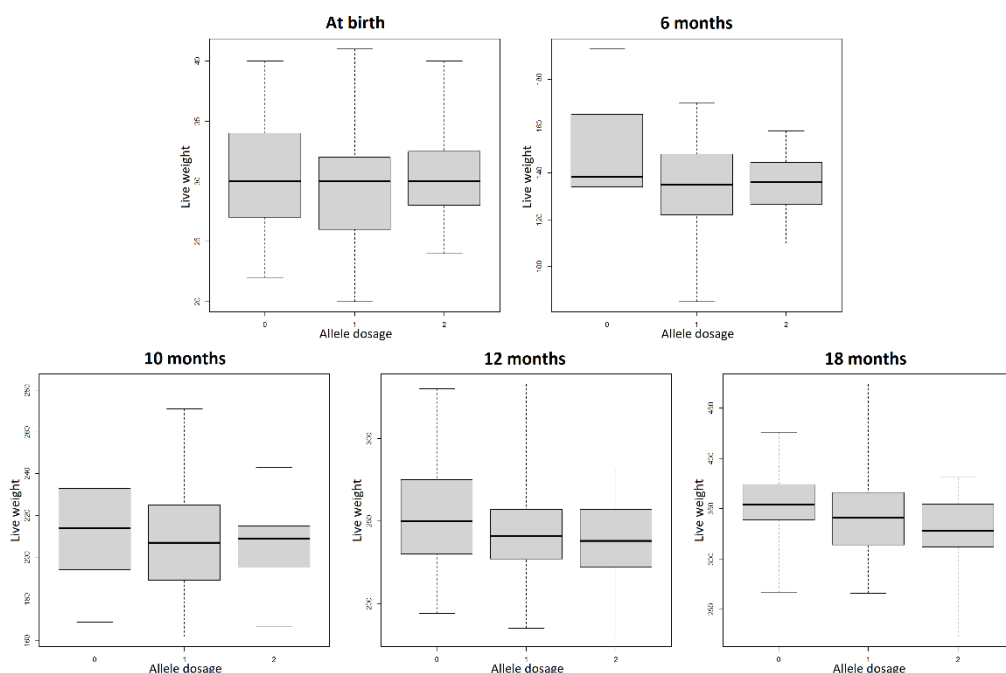


Fig. 1. Box and whisker plots illustrating the association between the dose of the methionine allele and the live weight of heifers of the Yaroslavl cattle breed at different ages

At the same time, because the system of reproduction in cattle is significantly different from panmixia, it can be assumed that the observed associations may be due to an unaccounted factor of the origin of animals. We conducted an additional analysis using pedigree data from animal records to verify this assumption. Using the “kinship” function of the R “kinship2” library, a kinship matrix 142×142 was constructed based on a genealogy spanning two generations (paternal and maternal grandparents). Then the principal component analysis was performed using the standard “eigen” R-function (Fig. 2).

We analyzed the association between the principal components and the live weight of animals at different ages. Overall, the strongest association with weight was found for the second component (PC2). It was statistically significant from 6 to 18 months. The association was strongest at the age of 18 months ($p=1.80E-06$). This is probably due to the fact that the PC2 component allows us to distinguish a cluster of animals that are descendants of the bull Marshal-1073 (Fig. 2), which apparently has a low breeding value for live weight, because 15 of its 16 daughters at the age of 18 months have a weight less than the sample average. Association in at least one of the ages was also observed for the 3rd, 4th, 5th, 8th, 10th, 15th and 18th components considering those accounting for more than 1 % of the variance explained. These components explain ~17 % of the total additive genetic variance. We used these components as covariates in the linear model in order to account for the effect of animal kinship in the association analysis.

As a result, the previously significant ($p < 0.05$) associations were retained. Moreover, the trend level association ($p < 0.10$) observed at 10 months of age reached a significant level after adjusting for principal components (Table 1). This suggests that the observed association does not represent a false-positive result due to the hidden effects of animal relatedness or sample stratification.

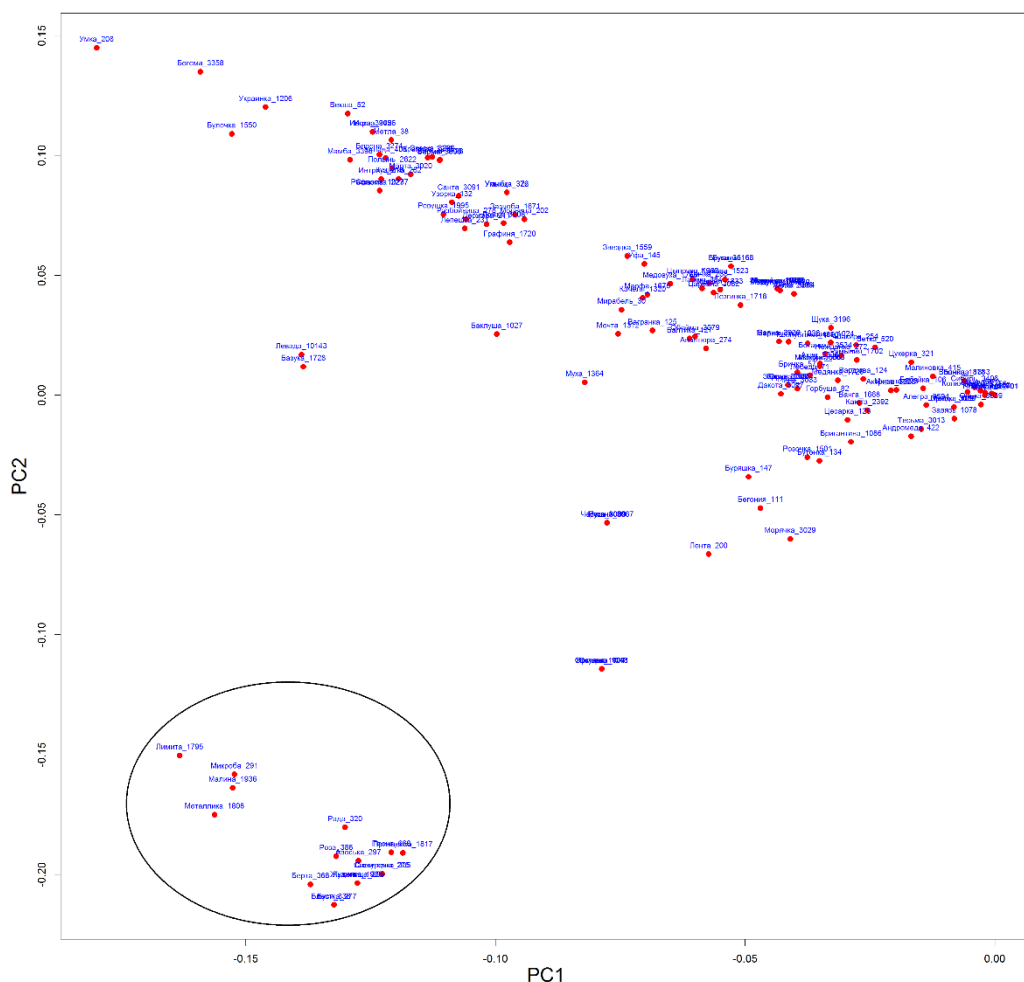


Fig. 2. Population structure of the analyzed sample visualized using two principal components. An oval in the lower left corner indicates a cluster of descendants of the bull Marshal-1073

Conclusion: The Yaroslavl cattle-specific Val105Met variant in the *KAT6B* gene is negatively associated with live weight of heifers at different ages. A further study exploring the relation of this mutation to other economically important phenotypes will elucidate its potential for use in marker-assisted selection.

Funding: The study is supported by the Kurchatov Genomic Center of the Institute of Cytology and Genetics of Siberian Branch of the Russian Academy of Sciences (Novosibirsk, Russia) according to the agreement with the Ministry of Education and Science RF. No. 075-15-2019-1662.

References

1. Yurchenko A., Yudin N. et al. Genome-wide genotyping uncovers genetic profiles and history of the Russian cattle breeds. *Heredity (Edinb)*. 2018;120(2):125-137. doi 10.1038/s41437-017-0024-3
2. Ruvinskiy D., Igoshin A. et al. Resequencing the Yaroslavl cattle genomes reveals signatures of selection and a rare haplotype on BTA28 likely to be related to breed phenotypes. *Anim Genet*. 2022;53(5):680-684. doi 10.1111/age.13230-x