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Monitoring and significance of the recessive genetic defect AH1 of Ayrshire cattle

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Abstract: Modern dairy farming is characterised by high selection intensity and the use of a limited number of bulls-producers. This increases the likelihood of widespread genetic defects in livestock populations. Genome-wide studies have identified DNA loci associated with the disruption of foetal embryonic development and its death, which have been called "fertility haplotypes". The aim of this study is to analyse the occurrence of AH1 haplotype or rs475678587 in Ayrshire bulls (n = 186) used in the artificial insemination system of Russia and to evaluate the reproductive and productive qualities of their daughters. The proportion of genetic defect carrier bulls in the analysed sample cohort was 16.66%. Analysis of the proportion of carriers of unwanted haplotype depending on the place of birth of the bull for service showed that the highest frequency was observed in bulls of Canadian origin (26.66%). Based on data on 97 478 cow and heifer calvings, stillbirth and abortion rates were analysed and cow reproduction rates were based on an AH1 status for the bull-father and bull for service. We observed a significant increase ($P < 0.05$ and $P < 0.001$) in the incidence of stillbirths when crossing the daughters of AH1-C bulls with AH1-C bulls. There was no negative association of abortion rates and reproductive qualities with AH1 haplotype. The high incidence of AH1 haplotype among animals of Ayrshire breed requires regular screening for the carriers of this haplotype not only among bulls, but also in cows.

Keywords: abortion; Ayrshire breed; genetic defects; haplotype fertility; stillbirth

In cattle breeding, the intensity of genetic selection is an important criterion. In this aspect, the high efficiency of herd reproduction allows to increase the annual calf crop, reduce the cost of culling of non-pregnant cows and cows with diseases of the reproductive system (Santos et al. 2018). One of the causes of economic losses is the interruption of pregnancy on different dates. The aetiology of abortion and stillbirth includes injuries, nutritional deficiencies, infectious diseases in cows (Gilbert 2019; Molefe and Mwanza 2019), as well as lethal recessive mutations (Zinovieva 2016). Genetic defects most often occur and accumulate within the same breed. Homozygous animals are unviable and rarely found in the population, but a defective allele can be transmitted to a significant number of offspring through heterozygous carriers. The degree of distribution of this phenomenon depends on the intensity of the use of mutant allele carrier sires (Denholm 2017).

Until recently, the registration of genetic anomalies has occurred only on the basis of a sufficient array of phenotypic data. Since the availability of genome-wide studies, it has become possible at the

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genome level to determine the DNA loci associated with impaired female fertility, as well as causing severe impairment of foetal development and death. According to Cole et al. (2015), from the 26 recessive haplotypes that have been registered and tracked in the US genomic grading system, 19 of them are fertility haplotypes. The frequency of these haplotypes varies from 0.01% to 13.00%. Frequency data may vary significantly from country to country.

In the Ayrshire breed, two fertility haplotypes AH1 (Ayrshire Haplotype 1) (Cooper et al. 2014) and AH2 (Ayrshire Haplotype 2) (Null et al. 2017) were discovered. According to the Canadian Dairy Network, analysis of pedigrees and genotyping of bulls made it possible to determine that the occurrence of the AH1 genetic defect over the past 35 years ranged from 17% to 30% (Van Doormaal 2017). The main reasons for the high prevalence of his haplotype in the Ayrshire breed are the use of a limited number of bulls for service, small population, high inbreeding and a decline in genetic diversity (Melka et al. 2013; Guarini et al. 2019).

The fertility haplotype AH1 of Ayrshire cattle is an autosomal monogenic genetic defect inherited by the recessive type. This genetic defect was first reported by Cooper et al. (2014). The genome-wide DNA scanning method mapped a region on BTA17 in the range of 65.9 Mbp to 66.2 Mbp associated with the reduction of cow fertility. An analysis of the data from 618 pairings showed a decrease in the conception rate by an average of 4.3 ± 2.5% for the carrier sire × carrier maternal grandsire crossing. The effect of AH1 on stillbirth rate was not evaluated due to insufficient data on calving. Analysis of pedigrees revealed the oldest bull – heterozygous carrier AH1. It was the bull Selwood Betty's Commander No. 31700, born in 1953. The intensive and widespread use of this bull and its descendants in the artificial insemination system contributed to the spread of AH1 haplotype in populations.

Later Venhoranta et al. (2014) found that AH1 is associated with the rs475678587 mutation in the *UBE3B* gene, which in a homozygous state causes the development of PIRM syndrome in calves (ptosis, intellectual disability, retarded growth and mortality). Replacement of the last nucleotide in exon 23 of the *UBE3B* gene (rs475678587 C > T) affects splicing. This leads to incomplete truncation of the HECT domain in the UBE3B protein and disrupts its function. UBE3B protein belongs to the ubiquitin E3-ligase family and plays a key role in a number of biological processes during organogenesis and neurodevelopment. The clinical implications of PRIM syndrome in calves have been described only by Venhoranta et al. (2014). These include ptosis, hypotension, developmental delays and mental retardation. Animals died at an early age or were euthanized due to the development of pathologies incompatible with life. In humans, loss-of-function mutations in the *UBE3B* gene cause severe permanent neurodevelopmental disorders which are phenotypically manifested by developmental delay, mental retardation, facial dysmorphisms (ptosis, blepharophimosis and telecanthus), hypotonia, microcephaly, newborn respiratory distress, gastrointestinal pathologies and hypocholesterolaemia (Basel-Vanagaite et al. 2012; Cheon et al. 2019). It was found that the mutation rs475678587 on BTA17 can be associated with AH1. Testing of 29 bulls by rs475678587 showed that 11 bulls that were carriers of the rs475678587 mutation also carried AH1, and 18 wild-type bulls did not have any AH1.

The death of calves and the loss of the foetus at various stages of pregnancy cause great economic losses in livestock (Cole et al. 2016). If the early death of the embryo is difficult to determine and can be regarded as an unsuccessful fertilisation, then a miscarriage in the later stages of pregnancy (in addition to the loss of the calf) causes a shift in the time of subsequent insemination and a prolonged reproduction cycle in the cow to 18 months or more, which can cause rejection of the animal. Thus, screening a population for genetic defects associated with signs of reproduction is an important task in the cattle breeding system.

The aim of this study is to analyse the occurrence of fertility haplotype AH1 or rs475678587 in the bulls of Ayrshire breed used in the artificial breeding system of Russia, as well as to assess the reproductive and productive quality of their daughters.

MATERIAL AND METHODS

The study includes 186 bulls of Ayrshire breed used for an artificial breeding system in the Russian Federation. The sample included 49 sires of Russian breeding enterprises available in catalogues (http://www.plem35.ru/ajrshirskaya-poroda.html, http://plembulls.ru/sites/default/files/files/ayrshiry.pdf, http://ppkarel.ru/katalog.html) 68 bulls from the database cdn.ca (https://www.

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cdn.ca/) and 69 bulls, findings which are obtained as a result of our own research (genotyping by sequencing for variant rs475678587). The analysis included bulls of the following origin: Finnish (n = 71), Russian (n = 47), Canadian (n = 45), Swedish (n = 14) and American (n = 9).

DNA isolation and genotyping of single nucleotide polymorphism rs475678587

DNA samples were obtained from bull sperm by phenol-chloroform extraction using mercaptoethanol. For amplification, primers were selected in the BLAST NSBI program (https://www.ncbi.nlm.nih.gov/) F: 5'-AGCAGCGGTCATTCTGTGAG-3' and R: 5'-CACTGTTGACCCCATTTCCG-3' (Eurogen CJSC, Moscow, Russia). The polymerase chain reaction (PCR) was carried out in 25 µl of the reaction mix containing 67 mM Tris-HCl pH 8.6, 2.5 mM $MgCl_2$, 16.6 mM NHOH, 0.125 mm of each of dNTP (dATP, dGTP, dCTP, dTTP) (SibEnzyme LTD, Novosibirsk, Russia), 0.5 µl of a primer, 50–100 ng genomic DNA and 2.5 pieces of a Taq DNA polymerase (SibEnzyme LTD, Novosibirsk, Russia) on an amplifier of Thermal Cycler T100 (Bio-Rad, Hercules, USA). The amplification mode included initial denaturation at 94 °C, then 35 cycles of 94 °C for 45 s, 60 °C for 45 s, 72 °C for 45 s, and a final extension at 72 °C for 5 minutes. The quality of the resulting PCR products was checked by electrophoresis on 1.5% agarose gel. Amplicon size was 250 bp. Sanger sequencing of the amplified fragment was performed on the Applied Biosystems 3500 Genetic Analyzer (Thermo Fisher Scientific Inc., Waltham, USA) using commercial BigDye Terminator v3.1 Sequencing Standard Kit (Applied Biosystems, Waltham, USA) sets according to the manufacturer's protocol. The amplicon sequences were analyzed using Mega-6 software (Kumar et al. 2018).

The test results were recorded using a short code: the first three characters related to the disease in question (AH1), and the last character indicated the test result: F (free) without the disease in question and C (carrier) – heterozygous carrier of the disease.

Statistical analysis of the results

The results of 97 478 calvings for cows and heifers were monitored for the period from 2003 to 2018. All cows and heifers were divided into groups depending on the genotype of the bull father or sire according to AH1: I – daughters of bulls AH1-C inseminated by bulls AH1-C; II – daughters of bulls AH1-C inseminated by bulls AH1-F; III – daughters of bulls AH1-F inseminated by bulls AH1-C; IV – daughters of bulls AH1-F inseminated by bulls AH1-F. The statistical analysis was carried out with DELL STATISTICA (data analysis software system) v13 Dell Inc. (2016, software.dell.com). ANOVA was performed at a significance level of $P < 0.05$ to determine differences in the mean values of variables between the analysed groups. A post hoc test was then conducted to characterize the significance between the results for the individual groups being compared. The value of $P < 0.05$ was considered statistically significant. Prediction of bull estimated breeding values in milk, fat and protein yield was performed using the mixed model equation shown in Kudinov et al. (2017) within BLUP Animal Model as follows:

$$y = X_1HYS + X_2DOAC + Z_{1a} + Z_{2pe} + e \quad (1)$$

where:

y – vector of the yield records;
HYS – vector of fixed effect (herd-year-season);
$DOAC$ – vector of fixed effect (days open – age calving);
a and pe – vector of random effects (animal and environment);
matrices X_1, X_2 and Z_1, Z_2 – relates fixed effects and random effects with the yield records;
e – vector of random residual effect.

The calculation of heritability was done using the formula:

$$h^2 = V_a/V_t \quad (2)$$

where:

h^2 – heritability estimate;
V_a – additive genetic variance;
V_t – total variance, calculated as the sum of additive, permanent environment and residual variances.

Reliabilities of the bull estimated breeding values were calculated using the method presented in Misztal and Wiggans (1988).

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The replication factor was calculated by the formula:

$$R = (V_a + V_{pe})/V_t \quad (3)$$

where:

R – replication factor;
V_a – additive genetic variance;
V_{pe} – environmental variance;
V_t – total variance.

Only animals with progeny were included in the sample. Phenotypic and pedigree data was obtained from "SELEX" database (LLC RC Plinor). The calculation of the inbreeding coefficient was done using the registered computer program "Selection and genetic statistics" ("SGS-VNIIGRZH") (Sergeev and Tulinova 2015).

RESULTS

For the entire sample analysed (n = 186), the proportion of bull-carriers of AH1 or rs475678587 was 16.66%. According to the results of genotyping of 69 studied bulls, 18 identified a heterozygous genotype from rs475678587 of the *UBE3B* gene (26.08%). All 49 bulls included in the analysis were free of the genetic defect of AH1 according to the catalogues and websites of domestic breeding enterprises. In the group of bulls, information on whom was obtained from the cdn.ca database (n = 68), 13 bulls (19.11%) were carriers of AH1.

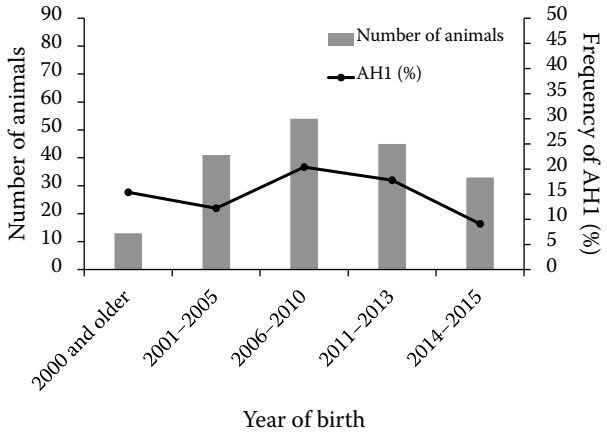

Figure 1. Frequency dynamics of the AH1 haplotype among the Ayrshire bulls used in the artificial insemination system of Russia, different birthdays

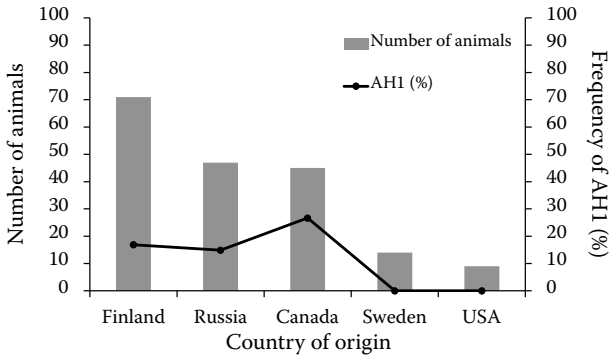

Figure 2. Carriage frequency of the AH1 haplotype among the Ayrshire bulls used in the artificial insemination system of the Russian Federation, depending on the locality of their breeding

A retrospective analysis of the occurrence of the AH1 haplotype in the analysed sample of Ayrshire bulls showed the maximum value in the group of bulls born in 2006–2010 (Figure 1). Among bulls born in 2014–2015, there was a decrease in the proportion of AH1-C animals by 11.28%. It may be due to the fact that since 2014 (from the moment of registration of the AH1 haplotype) genotyping for the carriage of AH1 has been available for Ayrshire bulls.

The results showed that the bulk of the bulls are of Finnish, Russian and Canadian origin. The share of bulls from the USA and Sweden was insignificant, and no AH1 carriers were detected among them. A high percentage of AH1 carrier bulls was found among animals of Canadian origin (26.66%), a lower percentage among Russian bulls (14.89%). The bulls of the Finnish selection occupied an intermediate position (16.90%). The data obtained indicate that it is necessary to strictly control the genetic material of bulls (Figure 2).

The calculation of the inbreeding coefficient according to the pedigrees of heifers lactating during the period 2014–2018 showed that against the background of an increase in the number of livestock and

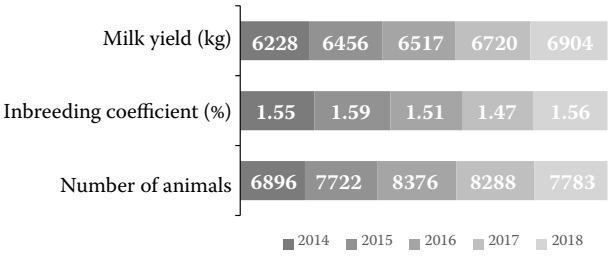

Figure 3. The level of inbreeding in the Russian population of Ayrshire cows

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Table 1. Estimated breeding values (EBV) of (non-)carrier bulls[1] for average milk, fat and protein yield

Trait	Bulls	
	AH1-F (n = 31)	AH1-C (n = 10)
Average (SD) number of daughters	611.4 ± 105.4	528.8 ± 110.0
EBV of yield of milk (kg)	227.7 ± 65.0	242.2 ± 127.3
EBV of milk fat (kg)	7.26 ± 2.20	6.71 ± 4.68
EBV of milk protein (kg)	–0.21 ± 1.64	–3.05 ± 1.81
Average reliability of EBVs	0.52	0.33

AH1-C = AH1 fertility haplotype carrier; AH1-F = non-carrier of the AH1 fertility haplotype
[1]The differences were not significant

milk yield, the inbreeding coefficient over the past five years did not exceed 1.59% (Figure 3).

A comparative analysis of the evaluation of bulls by milk productivity of daughters by the BLUP Animal Model did not reveal any reliable differences between bulls – heterozygous carriers of fertility haplotype AH1 and bulls free of the studied genetic defect (Table 1).

The results of a comparative analysis of the frequency of stillbirths and abortions, as well as the reproductive qualities of cows, taking into account the AH1 status of the bull-father and the bull for service, are shown in Table 2. An increase in the frequency of stillbirths for daughters of bulls AH1-C inseminated by bulls for service AH1-C was observed. These differences were significant when compared with other analysed groups ($P < 0.05$ and $P < 0.001$). No negative association of abortion rate and reproductive quality with the AH1 haplotype was found. Cows of group I (AH1-C × AH1-C combination) had significantly shorter open days ($P < 0.05$) and an insemination rate after the first calving ($P < 0.001$) in comparison with the cows of group IV (AH1-F × AH1-F combination).

DISCUSSION

Ayrshire breed in Russia is insignificant. The probability of accumulation of the load of genetic mutations in such a population is quite high. Despite the fact that, according to our data, the level of inbreeding for fresh cows did not exceed 1.56%, we observed a high frequency of the AH1 haplotype or rs475678587 among bulls, equal to 16.66%. Since the registration of the AH1 haplotype, its high occurrence has been noted in Ayrshire populations of different countries. Cooper et al. (2014) using a genome-wide scanning method (Illumina BovineHD, Illumina BovineSNP50, GoldenGate Bovine3K, Illumina BovineLD, GeneSeek Genomic Profiler, GeneSeek Genomic Profiler HD, BovineHD BeadChip) showed that the frequency of the AH1 haplotype was 26% in the USA Ayrshire population. In 2017 Null et al. using the method of genomic testing showed that the AH1 haplotype

Table 2. The results of calving and reproductive qualities of cows taking into account the AH1 status of father bulls and producer bulls

Parameter	Daughters of bulls AH1-C		Daughters of bulls AH1-F		P-value
	inseminated by bulls AH1-C	inseminated by bulls AH1-F	inseminated by bulls AH1-C	inseminated by bulls AH1-F	
Group	I	II	III	IV	
Number of calving	2 827	7 846	6 929	33 561	
Number of calves	2 847	7 909	7 037	34 109	
Abortion rate (M ± SEM)	0.007 ± 0.001	0.007 ± 0.001	0.006 ± 0.001	0.008 ± 0.000 4	0.760
Stillbirth rate (M ± SEM)	0.051 ± 0.004^{aA}	0.031 ± 0.009^{b}	0.031 ± 0.001^{B}	0.035 ± 0.001^{B}	< 0.001
Multiplicity of insemination to the first calving (M ± SEM)	2.04 ± 0.02	2.06 ± 0.01	2.08 ± 0.01	2.08 ± 0.008	0.410
Multiplicity of insemination after the first calving (M ± SEM)	1.76 ± 0.02^{A}	1.86 ± 0.01	1.84 ± 0.01	1.89 ± 0.007^{B}	< 0.001
Open days, days (M ± SEM)	127.29 ± 1.74^{a}	129.26 ± 1.04	132.95 ± 1.11	131.25 ± 0.51^{b}	0.013

AH1-C = AH1 fertility haplotype carrier; AH1-F = non-carrier of the AH1 fertility haplotype; M = mean
^{A,B}The differences are significant at $P < 0.001$; ^{a,b}The differences are significant at $P < 0.05$

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in USA Ayrshire cattle was found with a frequency of 22.2% (Null et al. 2017). Guarini et al. (2019) genotyped the Canadian Ayrshire population using the BovineSNP50 BeadChip and showed that the AH1 frequency was maximum for animals born in 2013 and was determined to be about 11.0%. AH1 Norwegian Red Cattle (NRC) study (Illumina BovineHD end Agena) shows that a mutation has entered the population in the last 10 years. Until 2005, the frequency of AH1 was close to zero and increased to 4–5% by 2018 (Gjuvsland and Holtsmark 2018). In studies by Venhoranta et al. (2014) in the Finnish population of Ayrshire (genotyped using the Illumina BovineHD Bead chip and subsequent Sanger sequencing), it was determined that rs475678587 polymorphism is the cause of PIRM syndrome and is associated with the AH1 haplotype. The rs475678587 mutation was found in 17.1% of the analysed Ayrshire bulls, which were also carriers of AH1. The chromosomal arrangement suggests that the presence of the rs475678587 mutation in the genome also implies the presence of the AH1 haplotype (Venhoranta et al. 2014). Genome-wide testing is needed to determine AH1 carriage, while rs475678587 polymorphism can be identified by AC-PCR or Sanger sequencing. In Russian studies, the available data on the AH1 frequency are based on the results of animal testing for rs475678587. In the research of Konovalova et al. (2020) the frequency of the AH1 or rs475678587 haplotype in various populations of Ayrshire cattle ranged from 6.33% to 26.09%.

The high incidence of AH1 or rs475678587 in the Russian Ayrshire breed can be attributed to the intensive use of two bulls: Poker No44563 (born in 2002) and Oblique No45678 (born in 2004), who according to available data of the Canadian Dairy Association are carriers of haplotype AH1. Although these sires are no longer used in the artificial insemination system of the Russian Federation, according to the website https://www.cdn.ca/ they received 3 593 and 2 662 descendants in total, including 2 470 and 1 890 daughters and 122 and 66 sons, respectively.

The widespread use of these sires is most likely due to their high genetic potential. According to an interstate domestic assessment in the Russian Federation of 58 Poker No44563 daughters for the period from 2014 to 2018 they exceeded peer productivity by 834 kg of milk while improving the quality of milk by 0.04% for fat and 0.16% for protein. Daughters of Oblique No45678 (n = 326), evaluated in the same period, also turned out to be better than the peers (+783 kg of milk, –0.01% fat, +0.11% protein).

According to Zinovieva (2016), the wide spread of genetic anomalies in cattle populations is facilitated by the fact that the carriers of lethal haplotypes are often bulls with high breeding value. In our study, there were no significant differences in milk production of bull daughters AH1-C and bull daughters AH1-F. Similar data were obtained from an analysis of US Ayrshire livestock (Cole et al. 2016). In selecting parental pairs, it is important to consider the status of animals for the carriage of genetic defects. There is a need to assess the genetic status of the AH1 haplotype not only in bulls, but also in cows. It is inappropriate to allow crosses of heterozygous carriers, since this can significantly reduce the fertility of herds. Calf mortality is an important problem on farms. Economic damage on farms is due not only to calf loss, but also to a number of costs for additional veterinary maintenance of the cow (Mahnani et al. 2018). Our data indicate that during insemination of the daughters of bulls AH1-C by bulls for service AH1-C, the stillbirth rate increases significantly, which is consistent with the data of Guarini et al. (2019). According to Storlien (2018), in NRC the proportion of stillbirths is approximately 2% higher in calves whose father and grandfather have AH1 (4.93%) than in calves whose father and grandfather do not have AH1 (3.11%).

CONCLUSION

The frequency of the AH1 haplotype in the sample of Ayrshire bulls used to improve herds in Russia was 16.66%. A high proportion of AH1-C bulls is of Canadian, Russian and Finnish origin. A significantly negative effect of the AH1 haplotype on the calf stillbirth rate during insemination of daughters of AH1-C bulls by AH1-C bulls was shown.

Conflict of interest

The authors declare no conflict of interest.

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