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ИЗВЕСТИЯ

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Қазақстан Республикасы Ұлттық ғылым академиясы "ҚР ҰҒА Хабарлары. Химия және технология сериясы" ғылыми журналының Web of Science-тің жаңаланған нұсқасы Emerging Sources Citation Index-те индекстелуге қабылданғанын хабарлайды. Бұл индекстелу барысында Clarivate Analytics компаниясы журналды одан әрі the Science Citation Index Expanded, the Social Sciences Citation Index және the Arts & Humanities Citation Index-ке қабылдау мәселесін қарастыруда. Webof Science зерттеушілер, авторлар, баспашылар мен мекемелерге контент тереңдігі мен сапасын ұсынады. ҚР ҰҒА Хабарлары. Химия және технология сериясы Emerging Sources Citation Index-ке енуі біздің қоғамдастық үшін ең өзекті және беделді химиялық ғылымдар бойынша контентке адалдығымызды білдіреді.

НАН РК сообщает, что научный журнал «Известия НАН РК. Серия химии и технологий» был принят для индексирования в Emerging Sources Citation Index, обновленной версии Web of Science. Содержание в этом индексировании находится в стадии рассмотрения компанией Clarivate Analytics для дальнейшего принятия журнала в the Science Citation Index Expanded, the Social Sciences Citation Index и the Arts & Humanities Citation Index. Web of Science предлагает качество и глубину контента для исследователей, авторов, издателей и учреждений. Включение Известия НАН РК в Emerging Sources Citation Index демонстрирует нашу приверженность к наиболее актуальному и влиятельному контенту по химическим наукам для нашего сообщества.

«ҚР ҰҒА Хабарлары. Химия және технология сериясы».

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REAL-TIME PCR TECHNOLOGY FOR CATTLE GENOTYPING BY *A* AND *B* KAPPA-CASEIN GENE ALLELES

Abstract. The main goal of the study was to develop and test an effective technology for cattle genotyping by the *CSN3* gene based on real-time PCR with hybridization-fluorescence detection. There was developed a method for real-time PCR for cattle genotyping by *A* and *B* alleles of the *CSN3* gene in the format of hybridization-fluorescence detection, involving the use of two 5′-fluorescence-labeled forward allele-specific primers, one reverse common primer, and one anti-primer labeled with a fluorescence quencher at the 3′-end of the oligonucleotide. As a result of practical studies aimed at testing the developed method, we obtained the technical result provided by the proposed technology, expressed in the effective identification of the desired genotypes due to correct interpretation of these curves of increasing fluorescence intensity, the results reliability of which was also confirmed by the well-known PCR-RFLP analysis technique for *Bos taurus* genotyping for similar allelic variants of the kappa-casein gene.

Key words: *Bos taurus*, PCR, RFLP, genotyping, allele, genotype, *CSN3*.

Introduction. The kappa-casein gene (*CSN3*) is one of the few known genes that is uniquely associated with the milk protein characteristics and milk technological properties. The *B*-allele of the *CSN3* gene in cattle is associated with a higher protein content in milk, a higher yield of cottage cheese and cheese, and better milk coagulation properties. Practice shows that high quality hard cheeses can only be made from milk obtained from cows with the *BB* kappa-casein genotype [1-5].

Along with the widely used method for assessing the allelic polymorphism of the *CSN3* gene in cattle based on PCR-RFLP analysis [6-8], SSCP-analysis [9-11], ARMS-PCR [12,13], allele-specific PCR (AS-PCR) [14,15], HRM analysis [16-18], and TaqMan real-time PCR [19,20].

Studies on the development of molecular genetic approaches to assessing the *CSN3* allelic polymorphism are relevant, are of scientific and practical interest due to the established economic value of the studied gene [21-23].

The develop and test an effective technology for cattle genotyping for the *CSN3* gene based on real-time PCR with hybridization-fluorescence detection is the main goal of the study.

Material and research methods. Testing of the developed method of real-time PCR for cattle genotyping for *A* and *B* alleles of the *CSN3* gene was carried out on DNA samples from 70 servicing bulls of the Elita in the Vysokogorsk region of the Republic of Tatarstan of the Russian Federation.

Nucleic acid extraction from cattle whole blood samples preserved with 10 mM EDTA-Na2 was carried out by the sorption method using a set of reagents for DNA isolation from clinical material "DNA-sorb B" (Central Research Institute of Epidemiology, Russia).

The technology of real-time PCR for cattle genotyping for *A* and *B* alleles of the *CSN3* gene was performed on a Rotor Gene 6000 amplifier (Corbett Research, Australia) according to the protocol shown in table 1.

Table 1 – Real-time PCR protocol for cattle genotyping for *A* and *B* alleles of the *CSN3* gene

Reagents	Initial concentration	Working concentration	1 sample	10 samples
dH_2O			13.6	136
dNTPs	2.5 mM	0.25 mM	2	20
Buffer	10×	1×	2	20
Taq DNA polymerase	5 units	1 units	0.2	2
CSN3-A	25 μM	0.25 μM	0.2	2
CSN3-B	25 μM	0.25 μM	0.2	2
CSN3-R	25 μM	0.5 μM	0.4	4
CSN3-S	25 μM	0.5 μM	0.4	4
DNA sample			1	
TOTAL			20	
Name and sequence of oligonucleotide primers: 5′-fluorescently-labeled forward *A*-allele-specific primer CSN3-A: 5′-FAM-ACT-GTA-GCT-ACT-CTA-GAC-GA-3′ (20 nt.) 5′-fluorescently-labeled forward *B*-allele-specific primer CSN3-B: 5′-VIC-ACT-GTA-GCT-ACT-CTA-GAT-GC-3′ (20 nt.) Reverse common primer CSN3-R: 5′-GCT-CTC-AAT-AAC-TTC-TGG-AGA-A-3′ (22 nt.) Anti-primer labeled with a fluorescence quencher at the 3′-end of the oligonucleotide CSN3-S: 5′-TCT-AGA-GTA-GCT-ACA-GT-3′-BHQ1 (17 nt.) Amplification Mode / [Hybridization Fluorescence Detection]: ×1: 94 °C – 4 min. ×30: 94 °C – 10 sec. 61 °C – 10 sec. 72 °C – 10 sec. 51 °C – 10 sec [Green detection channel for FAM fluorophore / Yellow detection channel for VIC fluorophore].				

The well-known technique of PCR-RFLP for cattle genotyping for *A* and *B* alleles of the *CSN3* gene [8] was carried out according to the presented in table 2 protocol.

Table 2 – PCR-RFLP protocol for *Bos taurus* genotyping for *A* and *B* alleles of the *CSN3* gene

PCR				
Reagents	Initial concentration	Working concentration	1 sample	10 samples
dH_2O			14	140
dNTP	2.5 mM	0.25 mM	2	20
Buffer	10×	1×	2	20
Taq DNA polymerase	5 units	1 units	0.2	2
JK5	25 μM	0.5 μM	0.4	4
JK3	25 μM	0.5 μM	0.4	4
DNA sample			1	
TOTAL			20	
Name and sequence of oligonucleotide primers: Forward primer JK5: 5′-ATC-ATT-TAT-GGC-CAT-TCC-ACC-AAA-G-3′ (25 nt.) Reverse primer JK3: 5′-GCC-CAT-TTC-GCC-TTC-TCT-GTA-ACA-GA-3′ (26 nt.) Amplification Mode: ×1: 94 °C – 4 min. ×40: 94 °C – 10 sec. 63 °C – 10 sec. 72 °C – 10 sec. ×1: 72 °C – 7 min.				
RFLP				
Reagents	Initial concentration	Working concentration	1 sample	10 samples
dH_2O			2.25	22.5
SE-buffer O	10×	1×	2.5	25
*Hinf*I	20 units	5 units	0.25	2.5
PCR product			20	
TOTAL			25	
Incubation at 37 °C for 3 hours.				

Detection of the PCR-RFLP result was carried out by horizontal electrophoresis in 2.5% agarose gel in TBE buffer (pH 8.0) containing ethidium bromide at a concentration of 0.5 μg/ml, followed by visualization of amplified products in an ultraviolet transilluminator (λ=310 nm), while hybridization-fluorescent detection of the PCR result with primers CSN3-A + CSN3-B + CSN3-R + CSN3-S is implemented in real time.

in silico PCR-RFLP profiles modeling: NEBcutter V2.0.

We also used reagents for molecular biological research produced by "SibEnzyme OOO" (Limited Liability Company) (Russia), "DNA-synthesis OOO" (Limited Liability Company) (Russia) and "Helikon OOO" (Limited Liability Company) (Russia).

Results and discussion. A technology was developed for real-time PCR for cattle genotyping for *A* and *B* alleles of the *CSN3* gene in the format of hybridization-fluorescence detection, involving the use of two 5′-fluorescently-labeled forward allele-specific primers (CSN3-A + SCN3-B), one reverse common primer (CSN3-R) and one anti-primer (CSN3-S), labeled with a fluorescence quencher from the 3′-end of the oligonucleotide.

The analysis of alignment of the nucleotide sequences of *A* and *B* alleles of the *Bos taurus CSN3* gene, flanked with the primers CSN3-A + CSN3-B + CSN3-R is shown in figure 1.

```
CSN3-A:  5′-FAM-ACTGTAGCTACTCTAGACGA-3′                          PCR-
CSN3-B:  5′-VIC-ACTGTAGCTACTCTAGATGC-3′                          product
Allele A: 01 5′-ACTGTAGCTACTCTAGAAGATTCTCCAGAAGTTATTGAGAGC-3′    42 bp
Allele B: 01 5′-..................C.....................-3′    42 bp
Anti-primer      ||||||||||||||||||   ||||||||||||||||||||||
CSN3-S: 3′-BHQ1-TGACATCGATGAGATCT-5′ AAGAGGTCTTCAATAACTCTCG-5′:CSN3-R
```

Figure 1 – Alignment of the nucleotide sequences of *A* and *B* alleles of the *CSN3* gene *Bos taurus*, flanked with the primers CSN3-A + CSN3-B + CSN3-R

A clear result of testing the proposed method for carrying out PCR in "real time" is shown in figure 2.

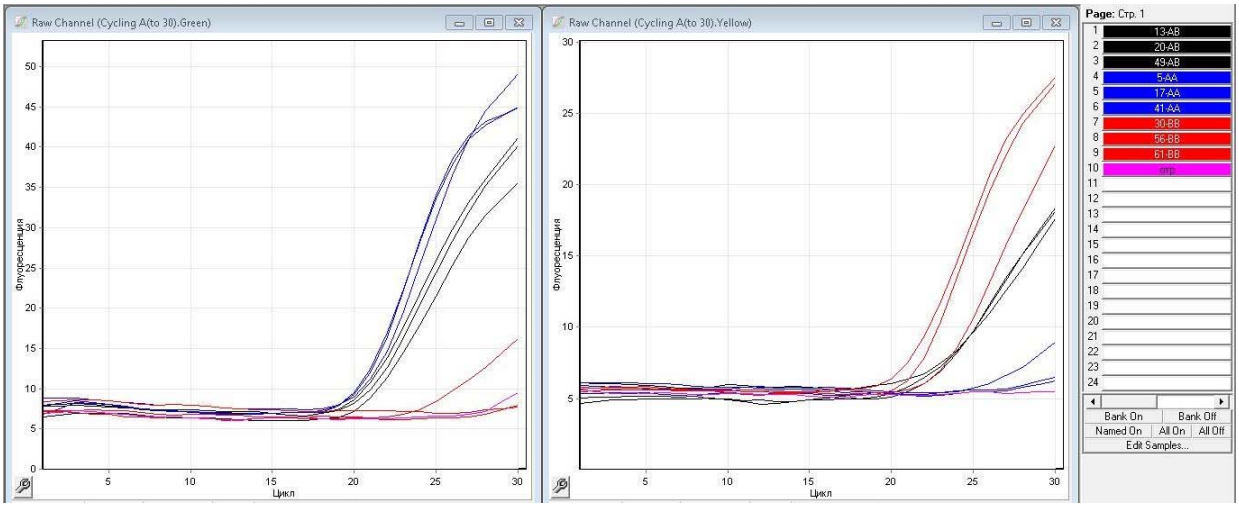

Figure 2 – The result of the developed technology of real-time PCR for cattle genotyping for *A* and *B* alleles of the *CSN3* gene (CSN3-A + CSN3-B + CSN3-R primers and CSN3-S anti-primer) Designations. Left - Green detection channel, Right - Yellow detection channel, Fluorescence growth curves for *AA* genotypes (blue lines), *AB* (black lines) and *BB* (red lines). OKO (pink lines).

As a result of practical research aimed at testing the developed technology of real-time PCR for cattle genotyping for *A* and *B* alleles of the *CSN3* gene in the format of hybridization-fluorescence detection, a technical result was obtained provided by the proposed method, expressed in the effective identification of the desired genotypes (*AA*, *BB*, *AB*) in view of the correct interpretation of these curves of increasing fluorescence intensity (figure 2).

The reliability of the obtained results was confirmed by the PCR-RFLP technique for cattle genotyping for *A* and *B* alleles of the *CSN3* gene.

The result of alignment and *Hinf*I-restriction mapping of the nucleotide sequences of *A* and *B* alleles of the *Bos taurus CSN3* gene locus flanked with primers JK5 and JK3 is shown in figure 3, where the amplified area of the DNA-target for the developed method of real-time PCR is highlighted in gray.

```
Gene/Allele      Primer JK5
CSN3/A      001 ATCATTTATG GCCATTCCAC CAAAGAAAAA TCAGGATAAA ACAGAAATCC CTACCATCAA
CSN3/B      001 .......... .......... .......... .......... .......... ..........
                **********.**********.**********.**********.**********.**********

Gene/Allele
CSN3/A      061 TACCATTGCT AGTGGTGAGC CTACAAGTAC ACCTACCACC GAAGCAGTAG AGAGCACTGT
CSN3/B      061 .......... .......... .......... ........T. .......... ..........
                **********.**********.**********.********.*.**********.**********

Gene/Allele                    HinfI
CSN3/A      121 AGCTACTCTA GAAGATTCTC CAGAAGTTAT TGAGAGCCCA CCTGAGATCA ACACAGTCCA
CSN3/B      121 .......... ....C..... .......... .........  .......... ..........
                **********.****.*****.**********.**********.**********.**********

Gene/Allele
CSN3/A      181 AGTTACTTCA ACTGCAGTCT AAAAACTCTA AGGAGACATC AAAGAAGACA ACGCAGGTAA
CSN3/B      181 .......... .....G.... ...T...... .......... .......... ..........
                **********.*****.****.***.******.**********.**********.**********

Gene/Allele                          HinfI
CSN3/A      241 ATAAGCAAAA TGAATAACAG CCAAGATTCA TGGACTTATT AATAAAATCG TAACATCTAA
CSN3/B      241 .......... .......... ....._____. .......... .......... ..........
                **********.**********.**********.**********.**********.**********

                                                                          PCR-
Gene/Allele                                                  Primer JK3   product
CSN3/A      301 ACTAGCGTAG ATGGATAAAT TAAATCTGTT ACAGAGAAGG CGAAATGGGC   350 bp
CSN3/B      301 .......... .......... .......... .......... ..........   350 bp
                **********.**********.**********.**********.**********

Gene/Allele GenBank A/N HinfI-restriction mapping HinfI-RFLP-profile
CSN3/A      AY380228    1-134/135-265/266-350 n.  134/131/85 bp
CSN3/B      AY380229    1-265/266-350 n.          265/85 bp
```

Figure 3 – Alignment and *Hinf*I-restriction mapping of nucleotide sequences of *A* and *B* alleles of the *CSN3* gene locus *Bos taurus* flanked with primers JK5 and JK3

The corresponding PCR-RFLP profiles generated as a result of *in silico* modeling are shown in figure 4.

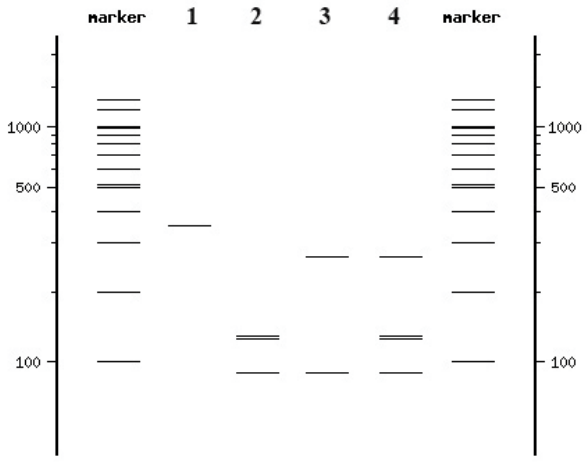

Figure 4 – *CNS3*-PCR-RFLP-*Hinf*I *Bos taurus* profiles (JK5 and JK3 primers)
Designations: 1) PCR product (350 bp); 2) *AA* genotype (134/131/85 bp [*Hinf*I]);
3) *BB* genotype (265/85 bp [*Hinf*I]); 4) *AB* genotype (265/134/131/85 bp [*Hinf*I]).

The electrophoretic picture of the well-known technique of PCR-RFLP for cattle genotyping for *A* and *B* alleles of the *CSN3* gene is shown in figure 5.

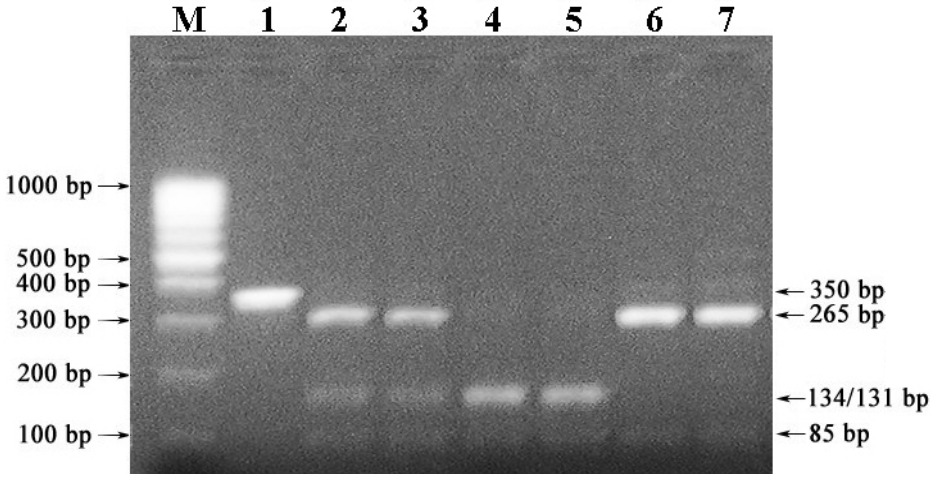

Figure 5 – Electropherogram of the PCR-RFLP result for cattle genotyping for *A* and *B* alleles of the *CSN3* gene with JK5 + JK3 primers and *Hinf*I endonuclease digestion with restriction enzyme
Designations: M) DNA markers 100 bp (SibEnzyme); 1) PCR product (350 bp); 2-7) generated *Hinf*I RFLP profiles: 2-3) *AB* genotype (265/134/131/84 bp); 4-5) *AA* genotype (134/131/85 bp); 6-7) *BB* genotype (265/85 bp).

As can be seen from Figure 5, JK5 and JK3 primers effectively initiate PCR amplification of the 350 bp *Bos taurus CSN3* gene locus, and subsequent *Hinf*I RFLP analysis of the generated genotype-specific fragments (*AA* = 134/131/85 bp, *BB* = 265/85 bp and *AB* = 265/134/131/84 bp) provides a correct genotyping procedure, which is justified by the calculated data of alignment, restriction mapping, and in silico modeling of the corresponding PCR-RFLP profiles.

The developed technology for real-time PCR for cattle genotyping for *A* and *B* alleles of the *CSN3* gene in the format of hybridization-fluorescence detection belongs to a variety of anti-primer-mediated quantitative real-time PCR, aQRT-PCR), proposed by J. Li & G.M. Makrigiorgos (2009) [24], capable of efficiently identifying single nucleotide polymorphisms.

The main difference between the proposed method and the closest analogue [25] is the design feature of 5′-fluorescently-labeled forward allele-specific primers, consisting entirely of gene-specific sequences, also competitively hybridizing with a complementary anti-primer of a shorter length, labeled with a fluorescence quencher with 3/-end of the oligonucleotide.

For the described technology of carrying out PCR, the introduction into each allele-specific primer of an unpaired nucleotide in the 3rd position from the 3′-end of the oligonucleotide is provided, which is typical for a variety of allele-specific PCR.

Conclusion. The technology of real-time PCR tested in this work for cattle genotyping for *A* and *B* alleles of the *CSN3* gene correctly identified the analyzed genotypes, the reliability of the results of which was confirmed by the well-known technique of PCR-RFLP analysis for *Bos taurus* genotyping for similar allelic variants of the kappa-casein gene. The proposed method is an express test that does not require time-consuming endonuclease cleavage procedures and subsequent electrophoretic separation of the generated fragments.

Р. Р. Вафин, Х. Х. Гильманов

Бүкілресейлік сүт өндірісі ғылыми-зерттеу институты, Мәскеу, Ресей

КАППА-КАЗЕИН ГЕНІНІҢ А ЖӘНЕ В АЛЛЕЛЬДЕР НҰСҚАСЫ БОЙЫНША *BOS TAURUS* ПТР-ГЕНОТИПТЕУДІҢ REAL-TIME ТЕХНОЛОГИЯСЫ

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ТЕХНОЛОГИЯ REAL-TIME ПЦР-ГЕНОТИПИРОВАНИЯ *BOS TAURUS* ПО ВАРИАНТАМ АЛЛЕЛЕЙ *A* И *B* ГЕНА КАППА-КАЗЕИНА

Аннотация. Основной целью исследования явилась разработка и апробация эффективной технологии генотипирования крупного рогатого скота по гену CSN3 на основе ПЦР в реальном времени с гибридизационно-флуоресцентной детекцией. Разработан метод ПЦР в реальном времени для генотипирования крупного рогатого скота по аллелям А и В гена CSN3 в формате гибридизационно-флуоресцентной детекции, включающий использование двух 5′-меченных флуоресценцией прямых аллель-специфических праймеров, одного обратного общего праймера и одного антипримера, меченного гасителем флуоресценции на 3′-конце олигонуклеотида.

Таким образом, апробированная в настоящей работе технология Real-Time-ПЦР-генотипирования кр.рог.ск. по вариантам аллелей *A* и *B CSN3* корректно идентифицировала анализируемые генотипы, достоверность результатов которых была подтверждена обще-известным техникой проведения ПЦР-ПДРФ-анализа для генотипирования *Bos taurus* по аналогичным аллелям гена каппа-казеина. Предложенный способ является экспресс-тестом, не требующим времязатратных процедур эндонуклеазного расщепления и последующего электрофоретического разделения генерируемых фрагментов.

Ключевые слова: *Bos taurus*, ПЦР, ПДРФ, генотипирование, аллель, генотип, *CSN3*.

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