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Original scientific paper

Investigation of the frequency of CWC15 gene mutation and its association with infertility

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ABSTRACT

The CWC15 gene encodes a protein that plays a role in mRNA splicing and facilitates the maturation of mRNA. Mutations occurring in the CWC15 gene can negatively impact embryonic development. In this study, we investigated the detrimental effect of a Single Nucleotide Polymorphism (SNP) called JH1, located in the CWC15 gene, on fertility in Jersey cattle. Samples were collected from 172 Jersey cows obtained from a limited number of Jersey farms in our country, including milk and saliva samples. The frequency of JH1 carriers and its association with infertility were determined through population screening using Polymerase Chain Reaction Restriction Fragment Length Polymorphism (PCR-RFLP) and DNA sequencing techniques. The study was conducted using randomly selected animals from the herd, without employing any exclusion criteria, and data obtained from the animal recording system. As a result, 9 out of 172 Jersey cows (5.23%) were identified as JH1 carriers. Although a correlation between JH1 and fertility was found, it was not statistically significant (P>0.05). Due to the economic loss caused by early embryonic deaths attributed to JH1, screening of imported Jersey semen and female animals can help prevent the increase of JH1 frequency in the entire population

Key words: CWC15 gene; JH1; PCR-RFLP; DNA sequencing

Introduction

Jersey cattle are a dairy breed and originate from the Isle of Jersey, situated in the English Channel between England and France. Jersey cattle are small in size and possess superior qualities in milk production. An adult female Jersey cow weighs approximately 400 kg on average. It is known that cows of this breed can produce around 3000 kg of milk containing about 5% fat. Jersey cattle are preferred as a breed and are widely used in developing countries through crossbreeding to enhance the milk yield of local cattle. Compared to Holstein

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cattle, Jersey cattle exhibit higher reproductive performance in terms of characteristics such as calving interval, milk productivity, early ages at first calving, and total number of births. When compared to the Holstein breed, the Jersey breed demonstrates higher reproductive efficiency. Reproductive features, such as calving interval, days open, age at first calving, and lifetime calf births, are at a higher level in Jersey cattle. First introduced to Turkey in 1958 from America, these cattle began to be raised in regions affected by the Black Sea climate, such as Samsun Karaköy Stud Farm (KOÇ and UĞURLU, 2020).

RNA splicing is one of the fundamental mechanisms of gene expression in eukaryotes. RNA splicing, defined as mRNA maturation, is a ribonucleoprotein complex known as the spliceosome, which consists of five small nuclear RNAs and numerous proteins coming together (CHEN and CHENG, 2012). NTC/Prp19 complex has been discovered to be protein complexes that exhibit activity dur- ing the catalytic activation in the spliceosome. The complex has been shown to be involved in transcription in Saccharomyces cerevisiae and to play a role in genome maintenance in higher eukary- otes. Consequently, the fact that it serves the same function in all species has led to the conclusion that it is a conserved complex (CHANARAT and STRÄßER, 2013). The Prp19 complex is believed to be a conserved essential component of the splicing machinery that facilitates the conformational changes undergone by the spliceosome during catalytic processes. The presence of the core proteins CWC15 and CDC5L in the Prp19 complex has been identified (VAN MALDEGEM et al., 2015) CWC15 encodes a highly conserved splicing factor universally expressed in eukaryotes. It has been primarily identified as a protein associated with the spliceosome in yeast and human cells (SLANE et al., 2020). Within the scope of cattle genome projects, single-gene (Mendelian) mutations have been detected (DAETWYLER et al., 2014). The the long-known dangerous recessive genetic disorder examples in cattle species include BLAD (Bovine Leukocyte Adhesion Deficiency) (IGNETIOUS et al., 2020), and mutations such as CVM (Com- plex Vertebral Malformation) (HACIHASANOĞLU and YARDİBİ, 2019) In a study conducted by VANRADEN et al. (2011), the presence of five different genetic structures leading to infertility was identified in three different dairy cattle breeds, namely Brown Swiss (1 individual), Holstein (3 individuals), and Jersey (1 individual) (VANRADEN et al., 2011). The specific genetic variation known as the Jersey haplotype (JH1) has been discovered in a region of the Bos taurus (BTA) autosome 15, spanning from 11 to 16 million base pairs (Mbp). This genetic variation has been found to have a impact on fertility. Interestingly, although the carrier frequency is relatively high at 23.4% in the population, no instances of individuals having two copies of JH1 have been observed. This suggests that JH1 is associated with loss of embryos, during development (SONSTEGARD et al., 2013). The causative mutation, in CWC15 (JH1) is a nucleotide polymorphism (SNP), for which it is possible to create a diagnostic test to identify individuals who carry this mutation. The CWC15 gene product facilitates the synthesis of the protein named Q2KJD3, which participates in the spliceosome structure responsible for the maturation of mRNA produced from DNA. A mutation in the CWC15 gene will prevent the related protein from carrying out its normal function, thereby impeding the completion of the spliceosome's task and the production of mature mRNA. The CWC15 gene is primarily expressed in the region referred to as the placental-uterine interface, particularly in the placenta (HUSON et al., 2020). The carrier status of the JH1 mutation in the CWC15 gene cannot be phenotypically identified. This situation implies that, during partner selection, particularly during insemination, both carrier-carrier pairings may lead to early embryonic losses, and carrier-normal pairings may contribute to an increase in the frequency of carriers within the population (HUSON et al., 2020). It is important to determine the frequency of this mutation in our country and to take the necessary measures, as this mutation, which is commonly observed at a rate of 20-25% in the U.S. Jersey population, may also be prevalent (ZHANG et al., 2015).

Our study has unique value as it represents the first research on DNA isolation from milk in Turkey, the first screening of the CWC15 gene JH1

mutation in Jersey breed animals in our country, and has the potential to provide information on the possible new mutation distribution in the identified target sequence. Additionally, it stands as the first study analyzing the relationship between the CWC15 gene JH1 mutation and infertility in Jersey breed animals in Turkey.

The primary aim of this thesis study was to accurately determine the frequency of the CWC15 (JH1) mutation using PCR-RFLP and DNA sequencing methods on DNA obtained from milk samples of cattle in our country. Additionally, the study aimed to determine the frequency of this specific haplotype.

Materıals and methods

Collection of milk samples. In our study, samples were collected from a Jersey farm located in the Aegean Region. From the farm, in addition to pedigree information on the Jerseys, data were obtained such as: their service periods, number of births (Table 1), the occurrence of pregnancy in which insemination, whether pregnancy was detected, if there was any early embryo loss, and pregnancy insemination rates. The data were evaluated for compatibility after the study. In the selected herd, samples were taken from breeding animals in which diseases causing embryo loss, such as Brucella abortus, foot-and-mouth disease, metritis, and endometritis, as well as infertility conditions such as polycystic ovaries and persistent corpus luteum, had been excluded. For this purpose, 15 ml of milk was collected from a total of 172 cows with available information. The collected milk samples were transported to the laboratory under cold chain conditions and stored at +4ºC until processing.

Collection of saliva samples. The animals, placed in the paddocks, were immobilized using the locking method. Saliva samples were taken from the cattle before their morning meals were given. This helped to ensure the oral cavity was relatively clean. The oral cavities were rinsed with normal drinking water.

Then, sterile swabs were rotated 4-5 times on the cheek area and under the tongue mucosa to collect saliva samples (ALHADDAD et al., 2019). For later use, the swabs were tightly closed in swab tubes containing isotonic solution, ensuring that the cotton part was submerged in the liquid. They were stored at +4°C and then at -20°C until the day of DNA extraction.

For the conventional PCR reaction, the following components were used to make the final reaction volume 25 µl: 1U Tag DNA Polymerase (Gene All, Lot: TQ016A28007), 0.2 mM dNTP mixture (Thermo Scientific, 25 mM), and 1X Tag Reaction Buffer (Gene All Lot: TB016G15000). The primers were used at a targeted concentration of 0.8 pmol. In addition, 3 µl of genomic DNA sample was added, and the required amount of dH2O was added to complete the total volume of 25 µl. For the amplification of the target DNA region, the PCR reaction, with a total volume of 25 µl, included 50-100 ng of genomic DNA, 10 pmol of each primer (forward and reverse), 200 µM of each dNTP, 2.5 ml of 10x PCR buffer solution, 1.5 µl of MgCl2, and 1U of Taq DNA polymerase enzyme. These amounts were adjusted to a final volume of 25 µl per sample by adding sterile water.

The primers used were as follows:

- Forward primer: 5′ TCTGCTTTAGG-GACTGAGGATGAAGTTGC 3′
- Reverse primer: 5′ GCTTTCACCCCA-CATTTAAAAGCAAACAAA 3′

The DNA was amplified with 35 cycles at 94°C for denaturation, 60°C for annealing, and 72°C for extension, followed by a final extension at 72°C for 5 minutes (initial denaturation at 95°C for 3 minutes).

Ethical approval was obtained from the Ondokuz Mayıs University Animal Experiments Local Ethics Committee on 20.04.2022 with the number E-68489742-604.02.03-238753.

RFLP PCR. The TaqαI restriction enzyme used in our study recognizes the T^CGA regions and cuts at its optimal temperature of 65°C in its own buffer. The DNA amplified at 65°C in 10-15 minutes using FastDigest Buffer, is cleaved. For each sample in our study, we prepared a mixture of 10 µl of PCR product, 2.5 µl of 10X FastDigest Buffer, 2.5 µl of 10X FastDigest Green Buffer, and 10 µl of sterile water to make a total of 25 µl. We incubated

this mixture at 65 degrees for 15 minutes, and then ran 10 µl of it on a 3% agarose gel and visualized it.

DNA sequence analysis. For DNA sequence analysis, a purification process was applied to separate the relevant portion of the CWC15 gene obtained from the PCR from primer residues and all other remaining DNA fragments. The added ddNTPs were radioactively labeled: green was chosen for ddATP, black for ddGTP, red for ddTTP, and blue for ddCTP radiation. Subsequently, the Thermal Cycler device was set at 95°C for 30 seconds, 50°C for 10 seconds, and 60°C for 4 minutes for 30 cycles. In each cycle, the DNA polymerase synthesized the template DNA in the 5'->3' direction until the ddNTPs were added. After the ddNTPs were added, the DNA polymerase terminated the DNA extension. This study was carried out using the PCR reaction products of the CWC15 gene, in a 2.5% agarose gel containing Bromophenol blue and glycerol (BBF, Lot: OLB00) in the loading and tracking buffer.

Statistical analysis. For the evaluation of data in the study, the Statistical Package for the Social Sciences (SPSS) 22.0 IBM (NY, USA) was used for statistical analysis. Categorical variables were expressed as percentage frequencies, while continuous variables were expressed as mean ± standard deviation. For group comparisons, the chi-square test was used for categorical variables, and the independent samples t-test was used for continuous variables.

*Qualitative determination of DNA***,** The 340 bp DNA fragment of the CWC15 gene was obtained in vitro using PCR. The DNA fragment, which was obtained in multiple copies in the PCR, was run on a 2.5% agarose gel at 150 V for 30 minutes and detected with UV light. For the evaluation of the results of the PCR products loaded onto the gel, a 100 bp marker was used in the first well. The gel image of the PCR result is provided in Fig. 1.

*PCR-RFLP analysis***.** The products amplified by PCR were subjected to the Taqα1 restriction enzyme using the PCR-RFLP method. The products were then run on a 2.5% agarose gel at 150 V for 30 minutes and analyzed with UV light. The analysis revealed that in individuals with the normal phenotype, 2 fragments (137-203 bp) were formed, while in individuals carrying the heterozygous mutant allele, 3 fragments (137-203 and 340 bp) were observed. A 100 bp DNA marker was used for the evaluation of the PCR-RFLP result. The gel image of the PCR-RFLP result is provided in Fig. 2.

In our study, 9 mutant individuals (5.23%) were found in 172 samples. These results are shown in Table 2. These cattle were divided into 3 and then 5 groups according to the number of days outside. JH1 mutation genotype distribution of the cattle according to the groups is given in Table 3.

It was found that the proportion of cattle with JH1 mutation heterozygous genotype increased as the number of days open increased (Table 3). The

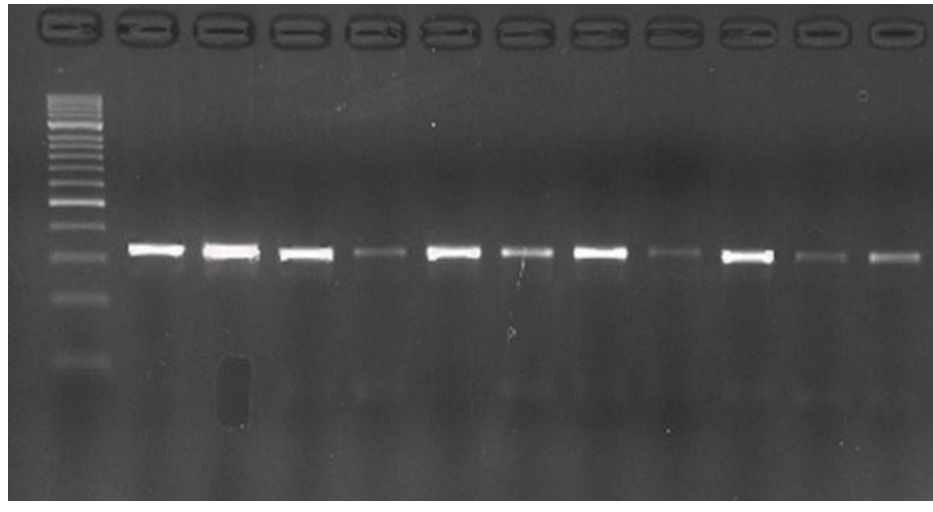

Fig. 1. Band samples of the CWC15 gene after PCR, run on a 2.5% agarose gel (using a 100 bp DNA marker)

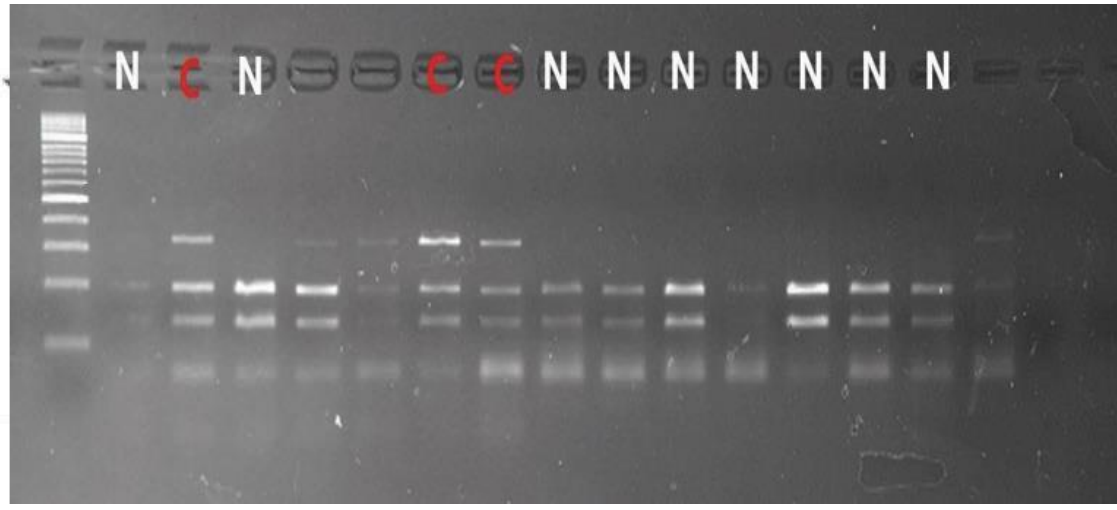

Fig. 2. Band samples of the CWC15 gene after cleavage on a 2.5% agarose gel
(N=Normal; C=Mutant)

Table 1. Distribution of calving numbers of sampled cows

Number of births	Frequency (n)	Rate (%)
Never given birth	33	19,9
Given birth once	57	34,3
Given birth twice	76	45,8

Table 2. PCR/RFLP results of the CWC15 gene

	Frequency (n)	Total (%)
Heterozygous mutant	9	5.23
Homozygous wild-type	163	94.77
Total	172	100.0

lowest proportion of cattle with JH1 mutation heterozygous genotype was found in the 0-90:1 group (Table 3). However, there was no statistically significant difference in the distribution of JH1 mutation genotypes between the groups of exposed on day 3 and exposed on day 5 (Table 3).

While the average number of pregnancies per age was 0.44±0.26 in normal genotype cattle with JH1 mutation, the average number of pregnancies per age was 0.33±0.24 in heterozygous genotype cattle with JH1 mutation. However, no statistically significant difference was found (P>0.05).

DNA sequence analysis. After the SNP in the codon encoding Arginine, the 54th amino acid in the 3rd exon of the CWC15 gene, the C/T transformation that causes this codon to turn into a stop codon was found by DNA sequence analysis. All of our DNA sequence analysis results were consistent with our PCR-RFLP results. DNA sequence analysis results are shown in Fig. 3 and 4.

Table 3. Distribution of JH1 mutation genotypes in cattle based on groupings

Group categories	Groups	JH1 mutations n=172		p
		Wild-type	Heterozygous	
“Days Open *	0-90: 1 n=96 (%)	93 (96.88)	3 (03.13)	>0.05
	90-180: 2 n=37 (%)	35 (94.59)	2 (05.41)	
	180- : 3 n=33 (%)	29 (87.88)	4 (12.12)	
Days Open**	0-90: 1 n=96 (%)	93 (96.88)	3 (03.13)	>0.05
	90-150: 2 n=31 (%)	29 (93.55)	2 (06.45)	
	151-210: 3 n=17 (%)	16 (94.12)	1 (05.88)	
	211-270: 4 n=13 (%)	11 (84.62)	2 (15.38)	
	271- : 5 n=11 (%)	10 (90.91)	1 (09.09)	

* Days open is the time from the birth of the cattle until the first pregnancy occurs or is detected. The study samples were evaluated in 3 different periods according to days open dates.
** Days open is the time from the birth of the cattle until the first pregnancy occurs or is detected. The study samples were evaluated in 5 different periods according to days open dates.

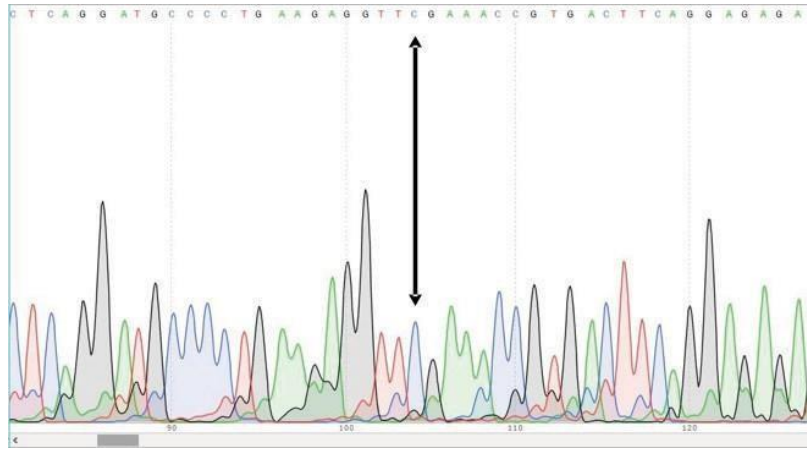

Fig. 3. Results of DNA sequence analysis for the normal genotype

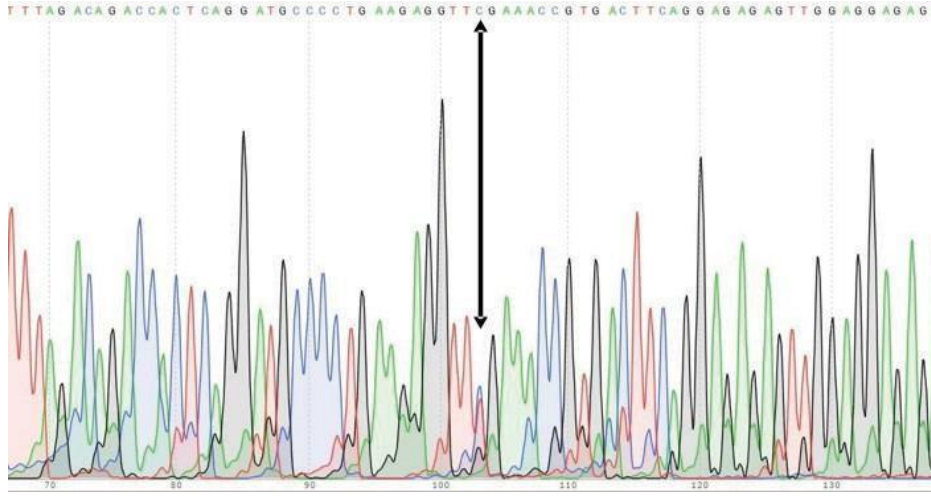

Fig. 4. Single nucleotide polymorphism obtained through DNA sequence analysis

Dıscussıon

The genetic defect known as Jersey haplotype 1 (JH1) leads to death, which in turn affects the reproductive efficiency of Jersey cattle (KUMAR et al., 2021). A genetic anomaly called JH1, which is inherited, has been linked to the occurrence of early embryo loss in Jersey cattle. Scientists have discovered that this anomaly is caused by a mutation in the CWC15 gene, where a cytosine is replaced with thymine. This mutation results in the change of an amino acid from arginine to a stop code (STRACQUADANİO et al., 2016).

In general, apart from the methods using blood samples for DNA extraction, DNA extraction from somatic cells obtained from milk samples, which are more suitable for animal welfare and do not cause stress to the animal, was preferred in our study. In addition, DNA was obtained from non-lactating or non-parturient animals by swab- bing the oral mucosa with the help of swabs and saliva. In our study, the PCR-RFLP method used by KUMAR et al. (2021) was preferred as a low cost and effective identification method. The PCR product of 340 bc using the same primers was finalised by 2.5% gel electrophoresis, which is one of the diagnostic methods of KUMAR et al. (2021).

Although homozygosity was expected between 7 and 90 individuals for 11 haplotypes, no homozygosity was observed in the study by VANRADEN et al. (2011). They confirmed the significant negative effects of 5 of the 11 defective haplotypes on conception rate in the phenotypic database, and also reported that 2.7% to 20.7% of the elite an- imals in their population in each breed were car- riers for the new defects, that there may be many additional lethal defects at a frequency too low to be detected in each breed, and also that the carrier frequency of the JH1 haplotype in the Jersey breed has been between 20% and 25% in the last 40 years (VANRADEN et al., 2011).

ZHANG et al. (2015) found 31 (6.9%) heterozygous individuals from 449 cattle imported to China from Australia. This rate was lower than the rate observed of between 20-25% in the American population. Out of 31 heterozygous carrier individuals, 20 of the sire bulls were descended from US bulls. As a result, they showed that US bulls have a high interaction with the Australian cattle population (ZHANG et al., 2015). SONSTEGARD et al. (2013) analysed 1612 stillbirths in the records obtained from the mating of JH1 carrier bulls with female offspring of JH1 carrier bulls, and found that there was no pregnancy loss after the sixtieth day. As a result, they associated JH1 mutation with early embryonic mortality (SONSTEGARD et al., 2013)

KUMAR et al. (2021) used two PCR based methods and proved their accuracy by comparing these two methods with the sequencing method. In the study, blood samples were taken from 30 Indian Jersey bulls. Using these genotyping tests for JH1 screening, 7 out of 30 Indian Jersey bulls were found to be carriers (23.3%). Randomly selected JH1 carriers and normal samples (non-carriers) identified by these double tests were confirmed by direct sequencing. JH1 originates from intensively utilised inbred ancestry, which is reported to have a high frequency (6.9%-23.4%). However, this selection was not found to be associated with milk traits (KUMAR et al., 2021).

As a result of our study, 9 JH1 haplotype carriers (5.23%) among 172 samples were determined by PCR-RFLP method. The PCR results of 172 samples were sequenced by DNA sequencing method, and the two methods were compared. Our results were in agreement with ZHANG et al. (2015) and KUMAR et al. (2021). However, since the animal data we obtained were not comprehensive enough, the association of haplotype with fertilisation was not found to be significant ($P>0.005$). In addition, when we analysed the pedigrees of 9 JH1 haplotype carrier animals in our study, it was determined that two carrier individuals were daughters of the same bull. Although there is no certainty because we do not have parental genotype data, it is highly probable that these two carrier siblings received this genetic inheritance from their father. Another finding we obtained during the analyses was that in one of our carrier samples, there was more than one homozygous normal individual born to the same bull, but from different mothers. Although we cannot be certain because we do not have parental genotypes, it is highly probable that this carrier received this genetic inheritance from his mother.

The fact that the animals in our sample population are over 3 years old at most and the number of births was low as a result, leads to a limitation of the data obtained (COLE et al., 2016). A study to be conducted in populations where the sample size and number of births are larger will give more meaningful results.

COLE et al. (2016) discovered the presence of 10 haplotypes for Holstein breeds, 1 for Ayrshire breeds, 5 for Brown Swiss breeds and 2 for Jer- sey breeds. They evaluated the effects of a total of 18 haplotypes on the yield characteristics of these breeds, such as: milk, milk fat, milk protein yield, somatic cell count, productive life span, birth rate and heifer conception rate. In their study, they revealed the presence of homozygous individuals for these haplotypes which cause early embryonic deaths in these breeds. In all of the studies carried out using different methods, no cattle carrying homozygous mutant alleles for haplotypes causing early embryonic deaths were found. Thanks to this study, they found significant results relating to the direct genetic effect on milk fat and protein, life span, female calf birth rate, cow conception rate and heifer conception rate, although no phenotypic effect was associated with JH1 carriers in Jerseys (COLE et al., 2016). In the study conducted by WU et al. (2020) 12 homozygous missing regions were detected in Jerseys. They found that 3 of these haplotypes had a negative effect on re-estrus after insemination, while 9 of them had no effect on re-estrus. Thus, they proved that 9 haplotypes did not cause early embryonic losses (WU et al., 2020).

In our study, no significant relationship was found between JH1 haplotype and infertility. This is due to the fact that our data and sample size were insufficient. However, significant relation- ships were found between the JH1 haplotype and infertility in other studies. In the herd used in our study, the average number of days spent outdoors was very high. This situation is not only due to JH1 mutation. Errors in insemination, various diseases, care and feeding errors, and the normal physiology of the animal, etc. can prolong the time spent in the open. In addition, unless JH1 carrier females are mated with a carrier bull, there may not be an extension in the service period due to JH1 haplotype. Therefore, imported or local Jersey semen should be analysed for this haplotype, and carrier bulls should be identified. Genotypic data should be obtained from female Jerseys. In this way, carri- er female and carrier bull matings will be prevent- ed. Our study is an important study in terms of informing about the CWC15 (JH1) gene mutation in Jerseys both in our country and in the world; and it is a major step that can benefit future studies on this breed. In addition, the results of this research are expected to provide a reference for the Jersey breed gene pool in Turkey. Imported semen purchases in Turkey and bulls bred in Turkey can be examined to ensure they are free from the CWC15 gene mutation. Management decisions to be taken about the Jersey breed for breed improvement can be evaluated from this point of view.

Ethics approval

Ethical approval was obtained from Ondokuz Mayıs University Animal Experiments Local Ethics Committee on 20 April 2022 with the number E-68489742-604.02.03-238753.

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Author’s contribution

Melih Sercan Ustaoğlu: ıdea/concept and design; Recai Aci: analysıs and/or ınterpretatıon, literature revıew, wrıter; Serbülent Yiğit: resources, materıals, data collectıon and/or processıng.

Declaration of competing interest

There is no conflıct of interest between the authors. This study is derived from the thesis.

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USTAOĞLU, M. S., R. ACİ, S. YİĞİT: Istraživanje učestalosti mutacije gena CWC15 i njegove povezanosti s neplodnošću. Vet. arhiv 95, 401-410, 2025.

SAŽETAK

Gen *CWC15* kodira protein koji sudjeluje u prekrajanju mRNA i njezinom olakšanom sazrijevanju. Mutacije koje se događaju u genu *CWC15* mogu negativno utjecati na embrionalni razvoj. U radu su istraživani štetni učinci jednonukleotidnog polimorfizma (SNP) nazvani JH1, smješteni u genu *CWC15*, na plodnost goveda. Uzorci mlijeka i sline prikupljeni su s farmi goveda od ukupno 172 krave pasmine Jersey. Učestalost nositelja JH1 i njegove povezanosti s neplodnošću u populaciji je određena primjenom lančane reakcije polimerazom i određivanjem polimorfizma dužine restrikcijskih fragmenata (PCR-RFLP) te tehnikama sekvenciranja DNA. Istraživanje je provedeno primjenom nasumičnog odabira životinja iz stada, bez primjene isključujućih kriterija, i na temelju baza podataka o životinjama. Rezultati su pokazali da je 9 od 172 krave pasmine Jersey (5,23%) identificirano kao nositelji JH1. Iako je uočena povezanost između JH1 i plodnosti, statistička znakovitost te povezanosti nije potvrđena (P>0,05). S obzirom na ekonomske štete uzrokovane ranom embrionalnom smrtnošću povezanom s JH1, probir uvezenog sjemena i ženki goveda pasmine Jersey može pomoći u prevenciji porasta učestalosti JH1 u cijeloj populaciji.

Ključne riječi: gen CWC15; JH1; PCR-RFLP; DNA sekvenciranje