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Journal of Agricultural Sciences
Journal homepage:
www.agri.ankara.edu.tr/journal

Monitoring of BLAD, DUMPS, CVM, BC and FXID in Turkish Native Cattle Breeds

Hasan MEYDAN[a] Mustafa UĞURLU[b] Mehmet Ali YILDIZ[a]

[a] *Ankara University, Faculty of Agriculture, Animal Sciences, Ankara, TURKEY*
[b] *Ondokuz Mayıs University, Faculty of Veterinary Medicine, Animal Sciences, Samsun, TURKEY*

ARTICLE INFO
Research Article – Animal Production DOI: 10.1501/Tarimbil_0000001211
Corresponding Author: Hasan MEYDAN, e-mail: meydan@ankara.edu.tr, Tel: +90(312) 596 14 32
Received: 19 December 2011, Received in Revised Form: 20 January 2013, Accepted: 27 January 2013

ABSTRACT

In this study, Turkish native cattle breeds were monitored with respect to the genetic disorders defined as bovine leukocyte adhesion deficiency (BLAD), deficiency of uridine monophosphate synthase (DUMPS), complex vertebral malformation (CVM), bovine citrullinaemia (BC) and factor XI deficiency (FXID). All these are autosomal recessive hereditary disorders causing serious economic losses in dairy cattle breeding throughout the world. In order to determine the presence or the absence of BLAD, DUMPS, CVM, BC and FXID genotypes in native cattle breeds, 200 heads of Anatolian Black, 100 heads of East Anatolian Red, 100 heads of Turkish Grey, 50 heads of Anatolian Southern Yellow, 50 heads of South Anatolian Red and 9 heads of Zavot breed (totally 509 heads) were sampled. Genomic DNA was obtained from blood and the amplicons were obtained by using PCR. PCR products were digested with *Taq*I, *Ava*I, *Eco*T22I and *Ava*II restriction enzymes for BLAD, DUMPS, CVM, and BC, respectively. Digested products of BLAD, DUMPS CVM and BC were analyzed by agarose gel electrophoresis. PCR products of FXID were analyzed by only agarose gel electrophoresis stained with ethidium bromide. The results demonstrated that no animals examined were the carrier of these genetic disorders. Thus, it can be concluded that mutant alleles of BLAD, DUMPS, CVM, BC and FXID are absent in Turkish native cattle breeds.

Keywords: BLAD; DUMPS; CVM; BC; FXID; PCR-RFLP

Türkiye Yerli Sığır Irklarının BLAD, DUMPS, CVM, BC ve FXID Genetik Kusurları Bakımından Taranması

ESER BİLGİSİ
Araştırma Makalesi – Hayvansal Üretim
Sorumlu Yazar: Hasan MEYDAN, e-posta: meydan@ankara.edu.tr, Tel: +90(312) 596 14 32
Geliş Tarihi: 19 Kasım 2011, Düzeltmelerin Gelişi: 20 Ocak 2013, Kabul:27 Ocak 2013

ÖZET

Bu çalışmada, Türkiye yerli sığır ırkları Sığır Lökosit Bağlanma Yetersizliği (BLAD), Üridin Monofosfat Sentezi Yetersizliği (DUMPS), Kompleks Omurga Deformasyonu (CVM), Sığır Sitrülin Birikimi (BC) ve Faktör XI Eksikliği (FXID) genetik kusurları bakımından tanımlanmıştır. Otozamal kromozomlar üzerinde bulunan resesif genlerle

belirlenmekte olan bu genetik kusurlar büyük ekonomik kayıplara neden olmaktadır. Araştırmada, Yerli Kara (200 baş), Doğu Anadolu Kırmızısı (100 baş), Boz ırk (100 baş), Güneydoğu Anadolu Sarısı (50 baş), Güneydoğu Anadolu Kırmızısı (50 baş) ve Zavot (9 baş) ırklarına ait toplam 509 baş sığır materyal olarak kullanılmıştır. Genomik DNA kandan elde edilmiş ve polimeraz zincir reaksiyonu (PCR) yöntemi ile üzerinde durulan genetik kusurlara ait gen bölgeleri çoğaltılmıştır. PCR ürünleri *Taq*I (BLAD), *Ava*I (DUMPS), *Eco*T22I (CVM) ve *Ava*II (BC) restriksiyon enzimleri ile muamele edilerek sığırların genotipleri agaroz jel elektroforez yöntemiyle belirlenmiştir. FXID genetik kusuru bakımından sığırların genotipleri ise sadece PCR ürünlerinin agaroz jel elektroforez yöntemindeki bant modelleri kullanılarak tespit edilmiştir. Araştırmada, incelenen 509 baş sığırdan hiçbirinin BLAD, DUMPS, CVM, BC ve FXID genetik kusurlarının taşıyıcısı olmadığı saptanmıştır. Bu araştırmanın sonuçlarına göre, BLAD, DUMPS, CVM, BC ve FXID mutant allellerinin Türkiye yerli sığır ırklarında bulunmadığı söylenebilir.

Anahtar Kelimeler: BLAD; DUMPS; CVM; BC; FXID; PCR-RFLP

1. Introduction

In animal breeding, genetic disorders are one of the most important issues for breeders. Due to the negative influence of such disorders on animals e.g. through abnormal anatomy or reduced production, breeders and breeding associations need to control the impact on the population. Currently, more than 50 genetic disorders and traits in cattle have been characterized in which the causative mutation has been identified at the DNA level.

Bovine leukocyte adhesion deficiency (BLAD), deficiency of uridine monophosphate synthase (DUMPS), complex vertebral malformation (CVM), bovine citrullinaemia (BC) and factor XI deficiency (FXID) are lethal autosomal recessive disorders known to affect Holstein cattle breed throughout the world. BLAD is characterized by greatly reduced expression of the heterodimeric β_2 integrin adhesion molecules on leukocytes resulting in multiple defects in leukocyte function. Defective leukocyte adherence leads to inadequate mucosal immunity (Kehrli et al 1990; Shuster et al 1992). Most cattle with BLAD die without having any diagnosis established, probably before one year of age. The molecular basis of BLAD is a single point mutation (A $\rightarrow$ G) of nucleotide 383 in the CD18 gene located bovine chromosome 1 (Tammen et al 1996; Nagahata 2004; Agerholm 2007).

DUMPS causes early embryonic mortality around 40 days during implantation in the uterus. It interferes with pyrimidine biosynthesis (Shanks & Greiner 1992; Kuhn & Shanks 1994; Kaminski et al 2005). In mammalian cells, the last step of pyrimidine nucleotide synthesis involves the conversion of orotate to uridine monophosphate synthase (UMP) and is catalyzed by UMP synthase enzyme. UMP synthase is necessary for the *de novo* synthesis of pyrimidine nucleotides, which are constituents of DNA and RNA. DUMPS is caused by single point mutation (C $\rightarrow$ T) at codon 405 within exon 5. The UMP synthase gene was mapped to the bovine chromosome 1 (Robinson et al 1993; Schwenger et al 1994; Citek et al 2006).

CVM, first discovered in the Danish Holstein population, is an inherited disorder with onset during embryonic development leading to frequent abortion of affected fetuses or perinatal death associated with vertebral anomalies (Agerholm et al 2001; 2004). Typical signs of CVM are a shortened neck and bilateral, symmetrical, moderate contraction of the carpal joints, severe contraction and slight lateral rotation of the fetlock joints. The hind limbs show marked bilateral, symmetrical contraction of the fetlocks with medial rotation of distal limbs. Malformation of multiple vertebrae, mainly involving those at the cervico-thoracic junction, is a common feature (Agerholm et al 2001; Nielsen et al 2003; Kanae et al 2005). CVM is caused by a missense mutation (G $\rightarrow$ T) occurring in the abnormal allele at position 559 in the gene SLC35A3 (solute carrier family 35 member 3)

located bovine chromosome 3 (Thomsen et al 2006; Rusc & Kaminski 2007).

BC, first described in the Australian Holstein population, prevents the synthesis of argininosuccinate synthetase that catalyses the conversion of citrulline and aspartate to argininosuccinate at the consumption of ATP (Robinson et al 1983; Harper et al 1986; Dennis et al 1989; Robinson et al 1993). Cattle affected by BC appear normal immediately after birth but die during the first 7 days of life. BC is caused by a transition of cytosine (CGA/arginine) into thymine (TGA/STOP codon) at codon 86 of the gene coding for argininosuccinate synthase leading to impaired urea cycle. The BC gene was mapped to the bovine chromosome 11 (Healy et al 1991; Grupe et al 1996; Healy 1996).

Factor XI is one of more than a dozen proteins involved in blood clotting. FXID may result in prolonged bleeding from the umbilical cord and anemia. Prolonged oozing of blood following dehorning or castration may also be observed. Affected cows frequently have pink-colored colostrum. Additionally, FXID causes reduced reproduction performance and the affected animals appear to be more susceptible to diseases such as pneumonia, mastitis and metritis (Gentry & Black 1980; Gentry 1984; Brush et al 1987). The causative mutation for FXID have been identified by Marron et al (2004) who found that the mutation consists of a 76 bp segment insertion into exon 12 in bovine chromosome 27. Consequently, BLAD, DUMPS, CVM, BC and FXID are important diseases that should be screened genetically to eliminate the mutant allele from the population.

According to archaeological, cultural and genetic evidences, Anatolia is one of the origins of domesticated cattle breeds. The earliest documented evidence for cattle domestication comes from Çatal Hüyük, a very large Neolithic site located in Anatolia (Perkins 1969). Also strong genetic evidences demonstrated that Near East including southeastern part of Anatolia is the origin of the European cattle breeds (Loftus et al 1999; Troy et al 2001).

Turkish cattle population is composed of exotic breeds (39%), crossbreds (41%) and native breeds (20%) (TurkStat 2011). The exotic breeds reared in Turkey are Black-White (Holstein), Brown Swiss, Jersey and Simmental. Turkish native cattle population consists of Anatolian Black, East Anatolian Red, Turkish Grey, Anatolian Southern Yellow, South Anatolian Red and Zavot. Although the productivity of Turkish native breeds is low, Turkish native cattle breeds are adapted to especially difficult local environmental conditions such as rough climatic conditions and insufficient food availability. Turkish native cattle breeds are potentially endangered because of crossbreeding. Therefore, Turkey has undertaken a national project (TAGEM-95K120250) titled "*In situ* Conservation Program of Livestock Genetic Resources" to conserve the Turkish native livestock breeds including cattle breeds.

Although BLAD, DUMPS, CVM, BC and FXID are specific to only Holstein cattle breed worldwide, Turkish native cattle breeds have not been previously described with regard to these genetic disorders except BLAD and DUMPS. This paper presents an overview of BLAD, DUMPS, CVM, BC and FXID in Turkish native cattle breeds. The aim of this study is to investigate whether or not there are mutant alleles of BLAD, DUMPS, CVM, BC and FXID in Turkish native cattle using PCR and PCR-RFLP method.

2. Material and Methods

Two hundreds heads of Anatolian Black, 100 heads of East Anatolian Red, 100 heads of Turkish Grey, 50 heads of Anatolian Southern Yellow, 50 heads from South Anatolian Red (Kilis) and 9 heads from Zavot cattle breeds (totally 509 heads) were randomly sampled from 9 different herds. Blood samples were collected from the jugular vein into EDTA-containing tubes, transported to the laboratory and stored at -20ºC until genomic DNA extraction, which was carried out by using a salting-out method (Miller at al 1988). Genomic DNA was stored at 4ºC until analysis.

Table 1- Primers, PCR product sizes and restriction enzymes (RE) used for identification of BLAD, DUMPS, CVM, BC and FXID genotypes

Çizelge 1- BLAD, DUMPS, CVM, BC and FXID genotiplerinin belirlenmesinde kullanılan primerler, PCR ürünlerinin uzunlukları ve restriksiyon enzimleri (RE)

Genetic disorder	***Primer***	***PCR Product sizes***	***RE***	***References***
BLAD	F: 5' GAATAGGCATCCTGCATCATATCCACCA 3' R: 5' CTTGGGGTTTCAGGGGAAGATGGAGTAG 3'	357 bp	*Taq*I	Meydan et al (2010)
DUMPS	F: 5' GCAAATGGCTGAAGAACATTCTG 3' R: 5'GCTTCTAACTGAACTCCTCGAGT 3'	108 bp	*Ava*I	Schwenger et al (1994)
CVM	F: 5' CACAATTTGTAGGTCTCAATGCA 3' R: 5' CGATGAAAAAGGAACCAAAAGGG 3'	233 bp	*Eco*T22I	Kanae et al (2005)
BC	F: 5' GGCCAGGGACCGTGTTCATTGAGGACATC 3' R: 5' TTCCTGGGACCCCGTGAGACACATACTTG 3'	198 bp	*Ava*II	Grupe et al (1996)
FXID	F: 5' CCCACTGGCTAGGAATCGTT 3' R: 5' CAAGGCAATGTCATATCCAC 3'	320 bp	-	Marron et al (2004)

The genotypes for BLAD, DUMPS, CVM and BC were identified by using PCR-RFLP method. After PCR, PCR products were digested with *Taq*I, *Ava*I, *Eco*T22I and *Ava*II restriction enzymes for BLAD, DUMPS, CVM and BC, respectively. The FXID genotypes were detected by only PCR method. All genotypes were determined using agarose gel electrophoresis stained with ethidium bromide. The primers, PCR product sizes and restriction enzymes used in this study for each genetic disorder were presented in Table 1.

To confirm the presence or absence of mutant alleles, control DNA samples from carrier and affected animals were used. The control DNA samples of BLAD and DUMPS carriers were obtained from University of Veterinary Medicine Hannover, Germany. The control DNA samples of CVM carriers and affected were obtained from University of Copenhagen, Denmark, while the control DNA samples of FXID carriers and affected were obtained from University of Illinois-Urbana, USA.

3. Results and Discussion

The primers used in experiment (Table 1) amplified successfully the DNA fragments of 357 bp, 108 bp, 233 bp, 198 bp and 320 bp for BLAD, DUMPS, CVM, BC and FXID, respectively. After digestion of the PCR products, the normal BLAD allele produced 2 fragments of 156 bp and 201 bp in unaffected animals. BLAD carriers exhibited 3 fragments of 156 bp, 201 bp and 357 bp. Normal DUMPS allele exhibited 3 fragments of 53 bp, 36 bp and 19 bp in unaffected animals. DUMPS carriers had 4 fragments of 89 bp, 53 bp, 36 bp and 19 bp. The normal CVM allele in unaffected animals (homozygous wild type) produced a single 233 bp fragment. The heterozygous animals (CVM carrier) exhibited 3 fragments of 233 bp, 212 bp and 21 bp. In homozygous CVM affected animals exhibited 2 fragments of 212 bp and 21 bp. The normal allele of BC produced 2 fragments of 109 bp and 89 bp. After PCR process, the normal FXID allele in unaffected animals produced a single 244 bp fragment. The fragment had a length of 320 bp in homozygous affected animals and FXID carriers exhibited 2 fragments of 244 bp and 320 bp.

The results of this study demonstrated that there was no carrier for BLAD, DUMPS, CVM, BC and FXID in 509 Turkish native cattle examined. It can be said that Turkish native cattle breeds examined are free from BLAD, DUMPS, CVM, BC and FXID alleles.

In this study, no animals examined were the carriers of BLAD, DUMPS, CVM, BC and FXID. This result could be explained by two ways: either mutations causing BLAD, DUMPS, CVM, BC and FXID do not exist in Turkish native cattle breeds or the sample size was not large enough to detect these genetic disorders in our study. Actually, these mutant alleles have been reported in only Holstein cattle throughout the world.

In previous studies (Akyüz & Ertuğrul 2006; 2008), BLAD and DUMPS alleles were not found in Turkish native cattle breeds. Similarly, BLAD, DUMPS, CVM and BC carriers were not found in Gir cattle in Brazil (Riberio et al 2000), in Polish dairy cattle in Poland (Kaminski et al 2005), in Brown Swiss bulls in Iran (Norouzy et al 2005), in Charolais, Limousine, Beef Simmental, Blonde d'Aquitaine, Belgian Blue, Aberdeen-Angus and Hereford cattle breeds in Czech Republic (Citek et al 2006) and in Jersey cattle, Indian cattle (*Bos indicus*) breeds, *B. taurus* x *B. indicus* crossbreds and the river buffalo (*Bubalus bubalis*) cattle in India (Patel et al 2007). All these reports and our findings supported the idea that these genetic disorders are specific to only Holstein cattle worldwide.

BLAD, CVM and FXID alleles were not found in Turkish native cattle breeds, whereas the carriers of BLAD, CVM and FXID were identified in Holstein cattle at low frequencies in previous studies. The frequency of mutant BLAD allele in Holstein cattle was estimated as 0.084 by Akyüz & Ertuğrul (2006), 0.035 by Meydan et al (2006) and 0.02 by Meydan et al (2010). The frequency of mutant CVM allele in Holstein cattle was calculated as 0.017 (Meydan et al 2010), while that of mutant FXID allele was estimated as 0.009 (Meydan et al 2009), 0.006 (Meydan et al 2010), 0.006 (Öner et al 2010) and 0.002 (Karslı et al 2011). In previous studies, DUMPS and BC alleles were not found in Holstein cattle (Akyüz & Ertuğrul 2006; Meydan et al 2006, 2010; Öner et al 2010) as well as Turkish native cattle breeds.

4. Conclusions

Our results demonstrated that the mutant alleles of BLAD, DUMPS, CVM, BC and FXID are absent in Turkish native cattle breeds. This is the first report on monitoring of CVM, BC and FXID in Turkish native cattle.

Acknowledgements

Authors wish to thank Y. G. Aydoğdu for helping in the part of collection and extraction of blood samples. Authors also wish to thank Dr. A. Wohlke (Institute for Animal Breeding and Genetics, University of Veterinary Medicine Hannover, Hannover, Germany), Dr. J. S. Agerholm, Department of Large Animal Sciences, Faculty of Life Sciences, University of Copenhagen, Denmark and Dr. J. E. Beever (Department of Animal Sciences, University of Illinois-Urbana, USA) for providing the control DNA samples. This study was partially supported by a grant from The Scientific and Technological Research Council of Turkey (Project No: TÜBİTAK-TOVAG-107O914; Project coordinator: Dr. M. A. YILDIZ).

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