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## Inherited diseases of Holstein cattle: Story so far in Turkey

### Review Article

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### ABSTRACT

Inherited diseases are caused by recessive alleles proceed from increased inbreeding in Holstein cattle population. Bovine leucocyte adhesion deficiency (BLAD), deficiency of uridine monophosphate synthase enzyme (DUMPS), complex vertebral malformation (CVM), factor XI deficiency (FXID) and bovine citrulinaemia (BC) are the most frequent inherited diseases in Holstein cattle population. The prevalence for carriers of BLAD, DUMPS, CVM, FXID and BC diseases were reported highest in Denmark (21.5%), USA (1.2%), Japan (32.5%), Turkey (18%) and Australia (13%) respectively. Moreover the highest prevalence for carriers of BLAD, CVM and FXID were reported as 2.2%, 3.4% and 18% respectively in Turkey so far. Neither DUMPS nor BC carriers were identified in Turkey so far. However further studies are required in order to identify the provinces that have risks for mutant alleles of inherited diseases in Turkey. Determining the carrier animals and exclude them from breeding is the only solution for eradication studies of inherited diseases.

**Keywords:** Holstein, inherited disease, BLAD, DUMPS, CVM, FXID, BC.

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## Introduction

Holstein is one of the mostly used cattle breed in dairy farming. In order to gain genetic improvement in Holstein cattle breeding, elite sires have been used intensively all around the world with artificial insemination (AI). The frequency of undesired recessive mutant alleles that cause to various inherited diseases, have been increased in Holstein cattle population as an outcome of inbreeding. Genetic diseases are usually caused by the inheritance of an absent or non-functional mutant gene. The homozygous animals for recessive mutant allele are affected by the disease. The heterozygous animals are responsible to transfer the inherited diseases to next generation and they are names as carriers. Mating between two carrier animals would genetically produce 25% of healthy, 50% of carrier and 25% of affected offspring. The development of molecular methods made possible to display the mutant alleles and identification of carriers. The aim of this review is to clarify the most frequent inherited disease of Holstein cattle and to notice their carrier prevalence determined so far in Turkey.

### Bovine leucocyte adhesion deficiency (BLAD)

Bovine leukocyte adhesion deficiency (BLAD) is also known as bovine granulocytopenia. Hagemoser et al. (1983) was first described the clinical signs of BLAD disease. The disease prevents neutrophil leucocytes to reach to the infection area by passing through the endothelial layer. Therefore altered neutrophil function resulting in the inability of the animal to initiate an inflammatory response in spite of high neutrophil counts. This disease is characterized with persistent and progressive neutrophilia, defective scarring, and increased sensitivity in first two years of life to infectious agents, infections of soft tissues such as gingivitis, ulcerative and granulomatous stomatitis, enteritis, pneumonitis, periodontitis, and death at 2 to 8 months of age. Affected calves are usually phenotypically normal at birth, but high fever, chronic diarrhea and other symptoms appears after a few weeks. Nagahata et al. (1987) classified BLAD as an autosomal recessive disorder and Kehrli et al. (1990) defined its molecular basis. In an affected calf, the expression of leukocyte  $\beta 2$  integrin molecules, that

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helps endothelial adhesion, decreases on leucocyte's cell surface. The disease is caused by a point mutation converts adenine to guanine in 383th nucleotide of CD18 encoding gene located in bovine chromosome 1. An aspartic acid to glycine substitution (D128G) was resulted with this point mutation in the adhesion glycoprotein CD18. The intensive use of elite Carlin-M Ivanhoe Bell (US1667366) and his father Pennstate Ivanhoe Star (US1441440) Holstein sires, caused to distribution of lethal recessive allele of BLAD (Shuster et al., 1992). The prevalence of BLAD affected and carrier animals was firstly reported as 0.5% and 21.5% respectively in Denmark by Jorgensen et al. (1993). Than the prevalence of BLAD carriers were reported from Japan (5.4%, Nagahata et al., 1993), Germany (13.5%, Biochard et al., 1995), France (10%, Taiunturier et al., 1995), USA (8.2%, Powell et al., 1996), Argentina (3.5%, Poli et al., 1996), Poland 0.8%, Natonek et al., 2000), Brasil (5.7%, Ribeiro et al., 2000), Iran (3.3%, Norouzy et al., 2005), India (3.2% in cows and 1.6% in bulls, Patel et al., 2007), China (0.5%, Li et al., 2011) and Macedonia (2.2%, Adamov et al., 2014). However it was reported by Nagahata et al. (1997), and Czarnik et al. (2004) that in a short time period the prevalence of BLAD carriers was increased in Japan (8.1%, Nagahata et al., 1997) and Poland (3%, Czarnik et al., 2004) and decreased in Germany (9.4% in 1997 and 8.3% in 2007, Schütz et al., 2008), Iran (0%, Hemati et al., 2015) and Pakistan (1.96%, Nasreen et al., 2009). Although BLAD carriers were reported from different countries, no carriers were found in Czech Republic (Citek et al., 2006) and Mexico (Riojas-Valden et al., 2009) so far.

#### **Deficiency of uridine monophosphate synthase (DUMPS)**

The uridine monophosphate synthase (UMPS) enzyme catalyzes converting orotic acid to uridine monophosphate in mammalian cells. Pyrimidine nucleotides compose the structure of DNA and RNA and UMPS is necessary for pyrimidine nucleotides synthesis. Deficiency of uridine monophosphate synthase (DUMPS) is caused by a single point mutation that substitutes cytosine to timin and leads to a premature stop codon at codon 405 within exon 5 of UMPS gene on bovine chromosome 1 (Patel et al., 2006). Embryos homozygous for mutant allele that cause to DUMPS usually die early in gestation, they do not survive to

birth. After 40 days of conception the embryos are usually aborted or reabsorbed, which leads to repeated breeding problems. Carriers have only half the normal activity of uridine monophosphate synthase, but they are phenotypically normal. The activity of the enzyme UMP synthase in in the liver, spleen, kidney, muscle and mammary gland is relatively decreased to about half of the normal value. Also carriers excrete an increased level of orotic acid in milk and urine. The distributor of the DUMPS carrier allele were Happy Herd Beautician and Skokie Sensation Ned (Kaminski et al., 2005). The prevalence of DUMPS carriers was reported in USA (1.2%, Shanks et al., 1990) and Argentina (0.96% bulls, 0.11% cows, Poli et al., 1996). No carriers were identified in Poland (Kaminski et al., 2005) and Czech Republic (Citek et al., 2006).

#### **Complex vertebral malformation (CVM)**

Complex vertebral malformation (CVM) was identified by Agerholm et al. (2001) in the Danish Holstein population. The ancestor of the undesired mutant allele was from US Holstein sire Penstate Ivanhoe Star (US1441440) and his son Carlin-M Ivanhoe Bell (US1667366) were showed as the worldwide distributors of the disorder by artificial insemination. The defect results from a point mutation that substitutes guanine to thymine at the 559th nucleotide of solute carrier family 35 member A3 (SLC35A3) gene. This mutation cause to conversion of valine to phenylalanine at position 180, is a critical amino acid divergence that abolishes the function of the nucleotide sugar transporter and results with vertebral malformations (Thomsen et al., 2006). The affected calves, are generally aborted (80%) or stillborn. Survived calves exhibit low birth-weight, cervical and thoracic vertebral anomalies, scoliosis and malformations in carpal and tarsal joints, also cardiac anomalies (Agerholm et al., 2004). The prevalence of CVM carriers were reported from Japan (32.5%, Nagahata et al., 2002), Germany (13.2%, Konersman et al., 2003), Sweden (23%, Berglund et al., 2004), Denmark (31%, Thomsen et al., 2000), Poland (24.8%, Rusc et al., 2007), Macedonia (11%, Adamov et al., 2014) and Iran (1.7%, Hemati et al., 2015). Decrease in prevalence of CVM carriers were notified in Japan (13%, Ghaum et al., 2008) and in Germany (8.3% in 2001 and 2.3% in 2007, Schütz et al., 2008). No CVM carriers were identified in Indonesia (Utami, 2015).

### Factor XI deficiency (FXID)

Factor XI is one of the blood clotting proteins. Factor XI Deficiency (FXID) may result in anemia with prolonged bleeding from the umbilical cord. Marron et al. (2004) have determined an insertion of a 76 bp segment into exon 12 of FXI gene (AT(A)28TAAAG(A)26GGAAATAATAATTCA) located on bovine chromosome 27 that was the causative mutation for FXID. The long strings of adenine (A) bases in the insertion, contains a stop codon and inhibits the full-length protein synthesis. Affected cows frequently have reduced reproduction performance, pink-colored colostrum, and susceptibility to diseases such as mastitis, metritis and pneumonia. Cattle that are homozygous and heterozygous for FXID mutant allele, might have lower calving and survival rates, since the estrous cycle of the affected cows is characterized by reduced follicular development and a slow process of luteolysis. The affected animals may survive for years with no other clinical signs in herd. Therefore FXID may have a significant economic loss on the dairy industry (Akyuz et al., 2012). The prevalence of FXID was reported from USA (1.19%, Marron et al., 2004), Japan (2.5%, Ghanem et al., 2005), India (0.2%, Rajeah et al., 2007) and Czech Republic (0.36%, Citek et al., 2008).

### Bovine citrullinaemia (BC)

Bovine citrullinaemia (BC) was firstly reported by Healey et al. (1990) after importation of semen from the US sire Linmack Kriss King to Australian Holstein population. The disease causes arginosuccinate synthetase (ASS) enzyme deficiency inhibits the conversion of citrulline to arginosuccinate in the course of urea metabolism. This situation causes to accumulation of citrulline, which is a more toxic product than ammonia during the process of urogenesis. The patient accumulates a high amount of citrulline in blood, cerebrospinal fluid, eye fluids and brain tissue. Bovine citrullinaemia is caused by a substitution of cytosine to thymine at codon 86 within exon 5 of the gene coding for ASS (Padeeri et al., 1999). Affected cattle by BC appear normal after birth. However the second day of life, affected calf looks depressed and there is no feed intake. The third day, calf often seen aimlessly roaming or standing with their head pressed against a wall. The disease progresses rapidly between the third and fifth day. The calf appears to be blind and finally collapses. Homozygous calves die during the first seven days of

life. The prevalence of BC carriers were reported from USA (0.3%, Robinson et al., 1993), Australia (13%, Heagle et al., 1996), and China (0.16%, Li et al., 2011). The BC carriers were not found in Germany (Grupe et al., 2006), Czech Republic (Citek et al., 2006) and India (Patel et al., 2006).

### The prevalence of carriers of Holstein inherited diseases in Turkey

There were various studies performed in order to determine the carriers of inherited diseases in Holstein cattle reared in different provinces of Turkey. The prevalence of carriers for these inherited diseases were summarized in Table 1.

In Turkey BLAD carriers were firstly identified in Kayseri (2.2%) by Meydan et al. (2009). Subsequently more carriers were reported from Ankara & Şanlıurfa (4%, Meydan et al., 2010), Antalya (2%, Sahin et al., 2013), Burdur (2%, Korkmaz Agaoglu et al., 2015), and Eskişehir (1.4%, Kaya et al., 2016). Furthermore the prevalence of BLAD carriers in Kayseri province was increased lately to 4.6% (Akyuz et al., 2015) which was the highest prevalence in Turkey. However no BLAD carriers were identified in Bursa province of Turkey (Oner et al., 2010).

No DUMPS and BC carriers were identified in Turkey so far (Akyuz & Ertugrul, 2008; Akyuz & Kul, 2009; Meydan et al., 2010; Oner et al., 2010; Kulaklı & Akyuz 2011; Karşlı et al., 2011; Sahin et al. 2013; Korkmaz Agaoglu et al., 2015; Kaya et al., 2016).

The FXID carriers were firstly reported from Bursa (1.2%, Oner et al., 2010) and thereafter more carriers were identified in Ankara & Şanlıurfa (1.2%, Meydan et al., 2010), Antalya (0.4%, Karşlı et al., 2011), Kayseri (0.7%, Yasar & Akyuz, 2012), İzmir & Ankara (1.7%, Akyuz et al., 2013), Burdur (18%, Korkmaz Agaoglu et al., 2015) and Eskişehir (0.9%, Kaya et al., 2016) provinces of Turkey. The prevalence of FXID carriers was determined highest in Burdur. No carriers were identified in Kırklareli, Edirne, Tekirdag and Istanbul provinces of Thrace region (Avanus & Altinel, 2016a).

The carriers for CVM in Turkey were firstly reported from Ankara & Şanlıurfa (3.4%) by Meydan et al. (2010). Avanus & Altinel (2016b) was reported that Thrace region of Turkey also contains CVM carriers (3.2%) including Kırklareli (6.6%), Tekirdag (1.9%), Istanbul (1.9%), and Edirne (1.7%) provinces. Kırklareli showed

**Table 1.** The prevalence of BLAD, DUMPS, FXID, BC and CVM carriers in Holstein cattle raised in various provinces of Turkey.

Region	Number of Holstein cattle (n)	The carriers' prevalence of					Reference
		BLAD	DUMPS	FXID	BC	CVM	
Antalya	504 cows	-	0%	0.4%	-	-	Karşlı et al., 2011
	504 cows	2%	-	-	0%	-	Sahin et al., 2013
Burdur	500 cattle	2%	0%	18%	0%	-	Korkmaz Agaoglu et al., 2015
Bursa	170 cows	0%	0%	1.2%	0%	-	Oner et al., 2010
Kayseri	136 cows	2.2%	-	-	-	-	Meydan et al., 2009
	150 cattle	-	-	-	-	0%	Kulakli & Akyuz, 2011
	150 cows	-	-	0.7%	-	-	Yasar & Akyuz, 2012
	262 cows	4.6%	-	-	-	-	Akyuz et al., 2015
Cattle Breeders' Association of Turkey & Kayseri	176 cattle	-	-	-	0%	-	Akyuz et al., 2008
Cattle Breeders' Association of Turkey	120 bulls	1.7%	-	-	-	-	Akyuz & Ertugrul, 2006
Cattle Breeders' Association of Turkey & Ankara	120 bulls	-	0%	-	-	-	Akyuz & Ertugrul, 2008
Ankara & Sanliurfa	225 cows & 125 cows	4%	0%	1.2%	0%	3.4%	Meydan et al., 2010
Izmir & Ankara	41 bulls & 18 bulls	-	-	1.7%	-	-	Akyuz, 2013
Eskişehir	219 cattle	1.4%	0%	0.9%	0%	-	Kaya et al., 2016
	287 cows	-	-	0%	-	-	Avanus & Altinel 2016a
Thrace region	311 cows	-	-	-	-	3.2%	Avanus & Altinel 2016b
Luleburgaz	21 bull	-	-	-	-	0%	Kepenek, 2007
Not mentioned	200 cows	-	0%	-	-	-	Akyuz & Çınar Kul, 2009

the highest prevalence for CVM carriers (Avanus & Altinel, 2016b). But no carriers were determined in Luleburgaz province (Kepenek, 2007).

The variations of prevalence's of carriers among each diseases (BLAD, FXID and CVM) might be sourced from the differences in sampling sizes, farms and regions in each study. Absence of mutant alleles of DUMPS and BC does not mean that Turkey is free from these diseases. Further studies should be performed in order to scan the mutant alleles in Holstein population of Turkey. Since if a genetic disease has finally been detected, the frequency of the recessive allele might have already increased in the population. In order to eradicate the inherited diseases, breeders in Turkey should always have a pedigree record, newborns should be registered carefully and defected calves' parents should be tested for suspected inherited diseases.

## Conclusion

The wide use of only a few elite sires has enhanced to increase in autosomal resessif inherited diseases with AI all around the world in Holstein cattle population. The most frequently reported inherited disease in Holstein

cattle were BLAD, DUMPS, CVM, FXID and BC. After improvement of molecular methods, various studies were performed all around the world in order to identify the carriers, exclude them from breeding and eradicate the inherited diseases from Holstein cattle breeding. The highest prevalence of BLAD, DUMPS, CVM, FXID and BC carriers were found in Denmark (21.5% Jorgensen et al., 1993), USA (1.2% Shanta et al., 2002), Japan (32.5% Nagahata et al., 2002), Turkey (18% Kormaz Ağaoğlu et al., 2015) and Australia (13%, Healge et al., 1996) respectively. The highest prevalence for BLAD, CVM and FXID carriers were 2.2%, (Meydan et al., 2009), 6.6% (Avanus & Altinel, 2016b) and 18% (Kormaz Ağaoğlu et al., 2015) respectively in Turkey. Among BLAD, DUMPS, CVM, FXID and BC diseases, FXID had the highest prevalence of carriers, but BLAD was the most studied one by the researchers from all around the world. Further studies should be performed in different regions and provinces for screening and controlling mutant alleles of BLAD, CVM and FXID diseases and before concluding that Turkey is null from DUMPS and BC mutant alleles.



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