Indian Journal of Animal Sciences **85** (8): 819–827, August 2015/Review article

Genetic disorders in dairy cattle: An Indian perspective

VIJAY KUMAR[1] and A K CHAKRAVARTY[2]

National Dairy Research Institute, Karnal, Haryana 132 001 India

Received: 26 September 2014; Accepted: 12 March 2015

ABSTRACT

Genetic diseases have always been present in the animal population but their significance has increased in recent decades. In some breeds, the occurrence of inherited anomalies has become frequent and economically important. Some of autosomal recessive disorders are Holstein specific. The present review article describes prevalence of the most important autosomal recessive disorders in Holstein and its crossbreds as compared to their occurrence worldwide. Mainly five disorders namely, bovine leukocyte adhesion deficiency (BLAD), deficiency of uridine monophosphate synthase (DUMPS), bovine citrullinaemia, complex vertebral malformation (CVM) and factor XI (FXI) deficiency syndrome, are being screened in Indian Holstein and its crossbred cattle with the major objective to reduce the incidence of genetic disorders in cattle population and reduce the economic losses to the organized farms. Detection of heterozygote carriers enables their selection, and therefore, the control and prevention of the spread of recessive diseases in the population.

Key words: BLAD, Bovine citrullinaemia, CVM, DUMPS, Factor XI Deficiency

India is regarded as a house of world's largest cattle population but most of them are considered to be poor producers as compared to exotic cattle. Among 37 major Indian breeds of cattle, there are only few milch breeds maintained for milk production and rest of them are neglected. Several cattle improvement programmes were initiated in the country to increase milk production of dairy animals. Key Village Scheme (KVS) and Intensive Cattle Development Projects (ICDPs) were among the first systematic attempts to improve the quality of cattle. Crossbreeding programmes of nondescript Indian cattle with exotic germplasm of Holstein Friesian, Jersey and Brown Swiss breeds, on field scale started in early sixties of 19th century with the launch of the ICDP. Crossbreeding gained momentum and economic relevance in the mid seventies. The spectacular increase in milk yield in the crossbred progenies generated overwhelming demand for crossbred cattle among cattle farming community that necessitated the expansion of the programme. As most programmes have merits and demerits, crossbreeding gave increase of milk production as merit and incorporation of new disorders in cattle as demerits. These introduced disorders are mainly genetic in nature.

A genetic disease is an illness caused by inborn abnormalities in genes. Most of them occur rarely and are of minor concern, but some increase in their frequency to the point that they become a significant economic concern and need to be selected against. Genetic abnormalities contribute to poor animal performance, structural unsoundness, semi-lethal or lethal disease etc. The most common inheritance pattern of genetic disease is as a simple recessive trait. The defective calf receives a recessive gene from its sire and dam. Testing of genetic diseases at young age will help in avoiding heavy economic losses. Therefore, it is necessary to study all the genetic diseases with its genetic cause, clinical symptoms and frequency of occurrence in general to find out possible strategies to counter them and avoid economic losses due to these diseases in dairy cattle. The objective of this review is to recapitulate recent findings and to give theoretical background of important congenital inherited diseases: Complex vertebral malformation, bovine leukocyte adhesion deficiency, deficiency of uridine monophosphate synthase, bovine citrullinaemia and factor XI deficiency.

Complex vertebral malformation

The complex vertebral malformation (CVM) is a recessively inherited congenital disorder leading to frequent abortion of fetuses or vertebral anomalies and prenatal death (Agerholm *et al*. 2001, 2004, Nielsen *et al*. 2003). It is characterized by growth retardation and bilateral flexure of the carpal and metacarpophalangeal joints along with rotation of the digits. In stillborn, aborted and preterm calves, CVM was characterized by shortened cervical and thoracic regions of the vertebral column and symmetric arthrogryphosis (Agerholm *et al*. 2001, Duncan *et al*. 2001).

Present address: [1]Assistant Professor (jaisvet@gmail.com), Department of Animal Genetics and Breeding, Pandit Deen Dayal Upadhyaya Pashu Chikitsa Vigyan Vishwavidyalaya Evam Go Anusandhan Sansthan, Mathura, Uttar Pradesh. [2]Principal Scientist (ak_chakravarty@yahoo.co.in), Dairy Cattle Breeding Division.

Multiple hemivertebrae, scoliosis and synostosis, fused and mis-shaped vertebral column have also been described. The syndrome was first discovered in the Danish Holstein population in 1999, but shortly thereafter, its occurrence was reported in Netherlands (Wouda *et al*. 2000), United States (Duncan *et al*. 2001), United Kingdom (Revell 2001) and in Japan (Nagahata *et al*. 2002). Genealogical records revealed that the calves suffering from CVM were genetically related to the US Holstein sire Penstate Ivanhoe Star (US1441440, born in 1963) and his son Carlin-M Ivanhoe Bell (US1667366) which had been used in dairy cattle breeding worldwide for two decades due to the superior lactation performance of their daughters. Consequently, the number of animals genetically related to the carrier bulls was very high and the disease-causing mutation was widespread among Holstein cattle throughout the world (Thomsen *et al*. 2006).

CVM is caused by a point mutation (missense mutation) from G to T at nucleotide position 559 of the bovine *solute carrier family 35 member 3* (*SLC35A3)* gene which causes valine to phenylalanine substitution at the amino acid level (Kanae *et al*. 2005). The *SLC35A3* gene encodes a Golgi-resident UDP-N-acetyl glucosamine transporter (Thomsen *et al*. 2006). UDP-N-acetyl glucosamine transporter transports nucleotide sugars from cytosol to Golgi body to use as a substrate for glycosylation of protein, lipid and proteoglycans (Guillen *et al*. 1998). Bovine SLC35A3 plays an immense function in the development of the axial skeleton, representing that a number of the molecular mechanisms that control during formation of vertebrae and ribs depend on carbohydrate modification in the golgi apparatus (Thomsen *et al*. 2006).

Studies of Danish Holstein showed that the extent of foetal mortality was approximately 77% prior to gestation day 260 (Nielsen *et al*. 2003). This is reflected in a significantly reduced ratio of CVM affected calves in breeding studies. Through increased foetal mortality, the status of the foetus has a significant effect on calving interval and involuntary culling of cows. The symptoms of the defect have not been observed in carriers of CVM (Agreholm *et al*. 2001). No productive and reproductive differences between carrier and non-carrier animals have been reported. The only difference which is very important was increase in the rate of intra-uterine mortality. The risk of return to service was higher in carrier animals (Berglund *et al*. 2004). Kumar *et al*. (2013a) reported that there was no significant difference between carrier and non-carrier animals for 3 month body weight of Karan-Fries calves.

To understand carriers of CVM and their probable significance in the economics of cattle breeding, Ghanem *et al*. (2008) compared the reproductive potential of CVM carrier Holstein cows in Japan with control groups. When studying the postpartum recommencement of ovulation—the carry-over of ovarian cycles after the birth of one calf—the researchers recognized that there was no major difference in the rate at which resumption occurs in carriers as compared to Holstein cows that were not carriers for CVM (Ghanem *et al*. 2008). However, CVM carrier cows were recognized to have drastically lower conception rates than control cows, with the gap between calves observed at 463 days in carriers as compared to 399 days for control cows, telling the possibility of heightened death of embryos in CVM carrier cows (Ghanem *et al*. 2008).

The disease was first discovered in the Danish Holstein population in 1999, but soon afterward reports documented the incidence of CVM in United States (Duncan *et al*. 2001), United Kingdom (Revell 2001), Netherlands (Wouda *et al.* 2000, 2001), Japan (Nagahata *et al*. 2002), Sweden (Berglund *et al*. 2004), Belgium (Mateusen *et al*. 2004) Czech Republic (Citek *et al*. 2006, 2008), Denmark (Thomson *et al.* 2006), Morocco (Boujenane and Ouhmama 2009), China (Chu *et al*. 2010, Wang *et al.* 2011, 2012, Zhang *et al.* 2012), Slovakia (Gabor *et al.* 2012) India (Kotikalapudi *et al.* 2013) and in Poland (Rusc *et al.* 2013). Berglund *et al.* (2004) estimated that 2,200 affected fetuses were produced yearly between 1995 and 1999 in Holstein population in Sweden, while the yearly loss in Germany was likely to be more than 8,000 fetuses between 1997 and 2000 (Konersmann *et al*. 2003). The flawed allele for CVM had reached in Holstein populations globally though widespread utilization of sires that afterward turned out to be carriers of the defect. Konersmann *et al*. (2003) reported that 13.2% of 957 sires used for insemination in Germany were found as carriers of CVM, while a prevalence of 31% and 32.5% was found in Denmark (Thomsen *et al.* 2006) and Japan (Nagahata *et al.* 2002). In Poland, out of the 605 bulls screened, 150 heterozygotes were diagnosed, including 118 that were progenies of known CVM carriers (Rusc and Kaminski 2007). Chu *et al*. (2008) by means of the polymerase chain reaction-single-stranded conformational polymorphism (PCR-SSCP) method, found 10 CVM carriers among 68 at-risk Chinese Holstein bulls and 282 carriers were found among 602 cows at-risk. Rezaee *et al*. (2008) found no carrier in Iranian Holstein bull. Ghanem *et al*. (2008) screened 200 Japanese Holstein crossbred cows and they found 26 (13%) cows were CVM carrier. Meydan *et al.* (2010) observed the mutant allele frequencies were 0.017 with corresponding carrier prevalence of 3.4% CVM in Turkey. In India, Mahdi *et al.* (2010a) examined 52 Holstein crossbred (KF) bulls and found that frequency of carriers was 20.35%. In the same herd 84 (76.36%) out of 110 at risk KF animals were found CVM carrier (Kumar *et al.* 2011a) and subsequently Yathish *et al.* (2011) reported that out of 55 KF male calves, none were CVM carriers.

Bovine leukocyte adhesion deficiency syndrome

Bovine leukocyte adhesion deficiency syndrome (BLAD) is an autosomal recessive hereditary disease affecting young Holstein calves characterized by recurrent bacterial infections, progressive periodontitis, ulcers of oral mucosa and impaired inflammatory responses (Kehrli *et al*. 1990, Nagahata *et al*. 1987, Kumar and Sharma 2009). These clinical findings are associated with impaired Neutrophil functions such as markedly decreased adherence,

chemotaxis and phagocytosis (Nagahata *et al*. 1987, Takahashi *et al.* 1987). In 1990, a lack of $ß_2$ integrin molecules expressed on the leukocytes from affected animals was found in a calf with granulocytopathy syndrome (Kehrli *et al*. 1990) and this disease was termed bovine leukocyte adhesion deficiency, which was considered to be analogous to human LAD. (Anderson *et al*. 1986, Kishimoto *et al*. 1989, Springer *et al*. 1984). Same deficiency syndrome is also called CLAD in dogs (Giger *et al*. 1987). BLAD causes immuno-depression in the early days of life. The animal is then sensitive to all infectious agents which can cause digestive, respiratory, cutaneous disorders and death. This disease is due to the absence of a protein $ß_2$ integrin at the surface of neutrophiles, which stops them from playing their role in non-specific defense of the animal.

BLAD was first identified in Holstein-Friesian cattle at the beginning of the eighties and no study has reported the occurrence and etiology of this disease in other breeds. The mutation found in the Holstein breed can be traced back to a heterozygote bull (Osborndale Ivanhoe), which due to its elevated genetic merit for milk production has been widely used in artificial insemination. This bull and its offspring (Penstate Ivanhow star - son and Carlin M Ivanhoe Bell - grandson) founded one of the main Holstein lineages. They are also responsible for spreading BLAD to several herd worldwide (Shuster *et al.* 1992). Affected cattle with BLAD were linked to common ancestral sires that had been documented to be carriers.

The molecular basis of BLAD is a single point mutation (adenine to guanine) at position 383 of the CD18 gene, which caused an aspartic acid to glycine substitution at amino acid 128 (D128G) in the glycoprotein. This mutation occurs near the centre of 26 consecutive amino acids that are identical in normal bovine, human, and murine CD18 and lies within a large extracellular region that is highly conserved across integrin ß sub-units (Kishimoto *et al*. 1989, Shuster *et al.* 1992). The other mutation, cytosine to thymine, between the normal and the BLAD allele detected at position 775 in the CD18 gene is silent (Shuster *et al.* 1992).

An experiment carried out to find out effects of the BLAD allele on milk, fat and protein yields, productive life and somatic cell scores. Data gathered from the Holstein Association, USA showed that carrier bulls were negative for all traits but significant only for protein (Powell *et al*. 1996). Same experiment also carried out in Taiwan and found milk production of BLAD-carriers was slightly higher than normal cows but somatic cell count was worse (Huang *et al*. 2001). In another investigation in Hungary, the relationship between bovine leukocyte adhesion deficiency (BLAD) genotype of bulls, their breeding value for milk yield, milk fat yield and milk protein yield and the milk yield of their daughters was studied. BLAD-carrier and healthy bulls were compared on the basis of their breeding value. The first 100 bulls ranked according to the total production index were used, including 9 BLAD carriers and 77 healthy sires with 2,835 and 21,950 daughters respectively. The BLAD genotype was not indicated for 14 bulls. The healthy animals significantly outperformed the BLAD carriers (Janosa *et al*. 1999). In a study, Kumar *et al.* (2013b) reported that there was no significant difference between carrier and non-carrier animals for three month body weight of calves.

BLAD carriers were among the most prominent bulls of the Holstein breed such as Osborndale Ivanhoe, Penstate Ivanhoe Star and Carlin-M Ivanhoe Bell (Powell *et al.* 1996, Shuster *et al*. 1992). Affected cattle with BLAD were linked to common ancestral sires that had been documented to be carriers (Jorgensen *et al*. 1993, Shuster *et al*. 1992). Several Holstein-Friesian bulls were identified as BLAD carriers and the gene encoding impaired CD18 spread to many countries.

Initially lack of efficient methods for identifying such type of genetic disorders and use of semen of proven carrier bulls lead to highest level of BLAD allele frequency in Holstein in US 23% (Shuster *et al*. 1992), France 10% (Tainturier *et al*. 1995), Germany (black and white HF 13.5% & red and white HF 0.3%) (Biochard *et al.* 1995), Argentina HF cattle 2.88% (Poli *et al*. 1996), Japan HF cattle 16% to 32% (Nagahata *et al*. 1997), Brazil HF 2.8% (defected); 5.7% (carrier) (Ribeiro *et al*. 2000). This disorder had also been reported from United Kingdom (Andrews *et al*. 1996), Hungary (Janosa *et al.* 1999), Korea (Chung *et al*. 1997), Lithuania (Kucinskiene and Miceikiene 2000), Uruguay (Llambi *et al*. 2003), Iran (Esmaelizad *et al*. 2002; Nassiry *et al*. 2005), Poland (Czarnik and Kaminski 1997), Denmark (Jorgensen *et al*. 1993), Austria (Schilcher *et al*. 1995) and India (Muraleedharan *et al*. 1999, Patel *et al*. 2007a, Mahdi *et al.* 2010b, Kumar *et al.* 2011b, Roy *et al.* 2012).

Shuster *et al*. (1992) tested 20 calves with clinical symptoms of LAD and found that all were homozygous for the D128G allele. In addition, 2 calves homozygous for the D128G allele were identified during widespread DNA testing and both were subsequently found to exhibit symptoms of LAD. The carrier frequency for the D128G allele among Holstein cattle in the United States was approximately 15% among bulls and 6% among cows. All cattle with the mutant allele were related to one bull, which through the use of artificial insemination sired many calves in the 1950s and 1960s. Screening of 4,000 dairy cows and heifer in US showed that, annually more than 16,000 to 20,000 recessive homozygote calves were born which were ultimately removed from population due to some infections (Biochard *et al.* 1995). Kehrli *et al*. (1991) tested 815 proven bulls and found that 10 bulls were BLAD-carriers. Biochard *et al.* (1995) tested 359 Holstein animals who were relatives and they found that this deficiency had been transmitting to next generation. Mortality rate in defective animals were 50% and 100%, respectively, in 2 month and 1 year old calves. Nagahata *et al*. (1997) tested 769 blood samples in Japan in 1994, 1995 and reported that the chances of born for BLAD are 0.16 to 0.32% respectively. Ribeiro *et al*.

(2000) estimated that the frequency of homozygous recessive animals was 2.8% and heterozygous animals were 5.7% in Brazil. Bulls (146) from artificial insemination stations and cows (192) kept in different regions of Lithuania were tested. Four bulls were found to be BLAD gene carriers. As their semen was widely used for cows' insemination in Lithuania, it resulted in 6.7% of BLAD frequency in dam population (Kucinskiene and Miceikiene 2000). Norouzy *et al.* (2005) tested 30 proven bulls in Iran and reported the frequency of carrier animals as 3.33%. In Turkey Akyuz *et al.* (2010) and Sahin *et al.* (2013) found 1.5% and 2% carriers in Holstein cows. In Chinese HF cattle BLAD-carrier frequency found to be 0.49% (Li *et al.* 2011). Adamov *et al.* 2014 found 2 carriers from 84 HF cow in Macedonia.

Patel *et al.* (2007a) examined 377 HF, 334 HF crossbred, 105 Jersey and 160 other breeds and found that frequency of carriers was only 3.23% in HF and its crosses in India. Mahdi *et al.* (2010b) examined 52 HF crossbred bulls and found that frequency of carriers was 7.31% in India. Kumar *et al.* (2011b) screened at risk KF animals and found that frequency of carriers was 21.82% in his sample. Yathish *et al.* (2010) examined 55 HF crossbred male calves and found that frequency of carriers was 3.64%. In a study by Khade *et al.* (2014), all the 50 HF crossbred cattle were found unaffected.

Deficiency of uridine monophosphate synthase

Deficiency of uridine monophosphate synthase (DUMPS) is a genetic disorder which interferes with pyrimidine biosynthesis. Uridine monophosphate synthase has a key role on the pyrimidine nucleotide synthesis, which is essential for normal growth and development for several ruminant and nonruminant species (Healy and Shanks 1987). Inactivation of this enzyme is caused by an autosomal-recessive heredity mutation, which occurs in the gene of UMPS. The mutation (C→T) leads to the loss of the restriction site of *Ava*I site in codon 405 of the gene (Schwenger *et al*. 1993). This disorder is named as DUMPS in the Holstein cattle and characterized by lowered blood activity of enzyme UMPS (Healy and Shanks 1987). DUMPS leads to embryonic death in early stage of pregnancy (Ghanem *et al*. 2006). So some serious reproductive problems take place in dairy herds.

The deficiency of uridine monophosphate synthase results in early embryonic death of homozygous offspring. In late 1987, the condition was declared an undesirable enzyme defect by the Holstein Association of America (HAA) and a screening programme was initiated by using a biochemical assay involving estimation of erythrocyte UMP synthase. Heterozygous or carriers have half of the normal activity of this enzyme (Shanks and Robinson 1990). Most of the DUMPS carriers identified in North America and Europe were the offspring of Happy Herd Beautician, a 5th best U.S. Holstein bull in 1987. Two HF carriers were found among 314 AI bulls in Hungary (Fesus *et al.* 1999). Mutation in the UMPS gene was also identified in 1.79% bulls, 0.96% cows in Argentina (Poli *et al*. 1996). Taiwan also reported two carrier out of 1468 HF animals screened for DUMPS (Lin *et al*. 2001a).

Several investigations were carried out in different countries (Kumar *et al.* 2010). No carrier animals were found among Holstein populations in Poland (Kaminski *et al*. 2005), Iran (Rahimi *et al*. 2006) and Turkey (Akyüz and Ertugrul 2008), but the mutant allele was detected in the studies carried out in USA (Shanks *et al*. 1987) and Argentina (Poli *et al*. 1996). Citek *et al.* (2006) screened 406 Holstein sires entering the AI programme in the Czech Republic from 2003–2005, no heterozygous sire for DUMPS was found. Patel *et al*. (2006) screened DUMPS in Indian Holstein cattle. The polymerase chain reaction-restriction fragment length polymorphism (PCR-RFLP) analysis was performed on a group of 642 animals, mainly HF and HF crossbred cattle, to identify carriers of these diseases. None of the animals were carriers of DUMPS. Sharma *et al.* (2013a) found none of the KF animals carrier of DUMPS in their study. Gaur *et al.* (2013) found one DUMPS carrier out of 86 Indian Holstein bulls.

Factor XI deficiency syndrome

Factor XI (FXI) deficiency is an autosomal recessive disorder (Kumar *et al.* 2011c), with partial deficiency of FXI coagulant activity in heterozygotes and considerable deficiency in homozygotes (Gentry and Ross 1994). One of the protein factors involved in blood coagulation is a serine protease – factor XI, also known as plasma thromboplastin antecedent. It is synthesized in the liver as a zymogen, and after conversion to a proteolytic enzyme, it participates in intrinsic or contact activation of the process (Gentry and Downie 1977). FXI deficiency was recognized in humans (Rosenthal *et al*. 1953) and cattle (Kociba *et al*. 1969, Gentry *et al*. 1975). FXI gene is located on chromosome number 4 in human (Asakai *et al*. 1987) and on chromosome number 27 in cattle. FXI gene encodes coagulation factor XI of the blood coagulation cascade and it is one of more than a dozen proteins involved in blood clotting.

In cattle, FXI-deficient animals may be asymptomatic or display several symptoms, like prolonged bleeding, anemia, greater prevalence of repeat breeding (Gentry and Black 1980, Brush *et al*. 1987, Liptrap *et al*. 1995), or even lower resistance to pneumonia, mastitis and metritis (Gentry *et al*. 1996). FXI deficiency has been identified in several species of mammals, including humans, dogs and cattle. In cattle, FXI deficiency has been described in Holstein cattle in Ohio and later in Canadian cattle, while some cases of hemorrhagic problems in British cattle have been reported. FXI deficiency may result in prolonged bleeding and anemia. Continued bleeding from the umbilical cord is sometimes seen in affected calves. Prolonged oozing of blood following dehorning or castration may also be observed. Affected cows frequently have pink-coloured colostrum. Blood in the milk led to the identification of the condition in a British dairy herd. Additionally, FXI

deficiency causes to reduced reproductive performance and affected animals appear to be more susceptible to diseases such as pneumonia, mastitis and metritis. Therefore, the presence of this genetic defect may have a significant economic impact on the dairy industry. Affected animals can survive for years with no overt clinical signs, even though they appear to have a higher mortality and morbidity rate.

In 1975, a herd of FXI deficient animals was established at the University of Guelph (Canada) by identifying heifers that were carriers and breeding them to a carrier sire. This herd has proven to be invaluable in studying the genetics of the condition and its consequences for health and reproduction. Selective mating established its mode of transmission. Affected animals have less than 10 % of normal biological activity of plasma factor XI, with most having less than 1%. Carrier animals have from 20 to 60% of normal levels, with a mean value of 38 + 10%. While affected animals can survive for years with no overt clinical signs, they do appear to have, as a group, higher mortality and morbidity. They are often referred to as "poor doers".

By using biochemical or genetic tests, the FXI deficiency was shown in Holstein cattle in the USA, Great Britain, Canada and Japan (Brush *et al*. 1987, Gentry *et al*. 1996, Marron *et al*. 2004, Ghanem *et al*. 2005). Marron *et al*. (2004) revealed that the molecular basis of coagulopathy in Holstein cattle is an insertion of a 76-bp adenine-rich fragment in exon 12 of the FXI gene. This insertion, composed of an imperfect poly-adenine tract [AT(A)28TAAAG(A)26G] followed by a duplicated region of the normal coding sequence [GAAATAATAATTCA], introduces a premature stop codon, which impairs the synthesis of functional protein.

Meydan *et al.* (2009) screened Holstein cows and study demonstrated that 4 out of the 225 Holstein cows tested in Turkey carried the FXI deficiency. Gurgul *et al.* (2009) tested 103 randomly selected cows, 28 cows with repeat breeding, and 9 cows with recurrent mastitis for the presence of an abnormal FXI allele. Three cows were diagnosed as carriers. Zhang *et al*. (2010) screened 576 Holstein cattle in China and found 2 carriers and one affected animal. Akyuz *et al*. (2012) compared the prevalence of FXI deficiency carriers in normally fertile and repeat breeder cows in Turkey. For this purpose, 161 Holstein cows were genotyped for the FXI gene mutation originating from various herds located in the Middle Anatolian region of Turkey. In the study, animals were divided into 2 groups – normally fertile (118) and repeat breeding (43) cows. Prevalence of the FXID carrier was found to be 0.85 and 2.33% in normally fertile and repeat breeder cows.

In India, Patel *et al*. (2007b) investigated the occurrence of FXI deficiency syndrome in Holstein-Friesian, Jersey, Indian cattle breeds, *B. taurus* × *B. indicus* crossbreds and the river buffalo *Bubalus bubalis*. A total of 1,001 dairy animals, mainly bulls, were genotyped to detect the mutation within gene encoding for factor XI. Two Holstein bulls were detected as heterozygous (carrier) for FXI deficiency, giving a carrier frequency of 0.6% in Indian Holstein cattle. None of the other cattle was found to be a carrier for FXI. In a study carried by Azad *et al.* (2011) in India for screening of 253 Sahiwal cattle and 200 Karan-Fries cattle, none of the animal found affected or carrier.

Bovine citrullinaemia

Bovine citrullinaemia is a genetic disorder, which has been reported in Holstein cattle (Fesus *et al*. 1999). It has been established that bovine citrullinaemia is a consequence of a deficiency of argininosuccinate synthetase (ASS), one of the enzymes of the urea cycle. A deficiency of the urea cycle enzyme results in a lethal neurological disease in newly born calves. The urea cycle involves a series of biochemical steps in which nitrogen, a waste product of protein metabolism, is removed from the blood and converted to urea. The deficiency of ASS occurs when a calf inherits a copy of the mutant gene encoding for ASS from each parent. The gene is located on chromosome Number 11 (BTA11). The mutation is caused by a transition of cytosine to thymine at codon 86 within exon 5 in the gene coding for ASS leading to impaired enzyme, which cannot participate in urea cycle (Dennis *et al*. 1989). Calves affected with the disease appear normal immediately after birth. However, by the second day of life they become depressed and feed poorly. By the third day, they are often seen aimlessly wandering about their enclosure or standing with their head pressed against a fence or wall. Between day 3 and 5 the disease progresses rapidly. The calves appear to be blind and then they collapse. Death usually occurs within 12 hours of onset of these clinical signs (Healy *et al*. 1990). The clinical signs of citrullinaemia are believed to be as a consequence of accumulation of ammonia in the brain of the affected calves.

Bovine citrullinaemia was reported in Australia (Harper *et al*. 1986) and the mutation responsible traced to a North American sire named Greyview Crisscrossh, the semen of whose son Linmack Kriss King (LMKK) was used extensively in Australia (Healy *et al*. 1991). However, no carriers were found black and white cattle in Germany (Grupe *et al*. 1996), Korea (Lee *et al*. 2002), India (Patel *et al*. 2006), Czech Republic (Citek *et al*. 2006), Turkey (Oner *et al*. 2010, Sahin *et al.* 2013) and Iran (Eydivandi *et al*. 2012). Many carriers were detected in Australia (Healy *et al*. 1991), USA (Robinson *et al*. 1993), India (Muraleedharan *et al*. 1999), Hungary (Fesus *et al*. 1999), Taiwan (Lin *et al*. 2001b) and China (Mei *et al*. 2009, Li *et al*. 2011). In India, Gaur *et al*. (2012) performed analysis on a group of 120 Holstein bulls to identify carrier (heterozygous) animals. Two out of 120 (1.67%) animals were found carrier for bovine citrullinaemia. Sharma *et al.* (2013b) in their study found none of the Karan-Fries animal carrier for bovine citrullinaemia.

The genetic disease causes heavy losses because of poor animal performance; structural unsoundness reduces the production and reproductive potential of the animal. The massive spread of genetic defects like CVM and BLAD in

recent years is caused by the extensive use of elite carrier sires. Artificial insemination accelerates the spread of undesirable recessives world-wide. However, the new methods of molecular genetics enable us to find the cause at gene level. This makes it possible to detect heterozygous animals and to control the genetic health of the population. Use of molecular methods into animal research promises quick progress in animal potential. This review demonstrated cases of presence of disorders; BLAD, DUMPS, CVM, Bovine citrullinaemia and FXI in Holstein and Holstein crossbred population which could have been enough to spread unwanted gene in the population. If no cases are observed in routine investigation even then an extensive screening programs for detection of genetic disorders seems necessary to ensure the utilization of bulls free from genetic disorders for artificial insemination programmes in India.

REFERENCES

Adamov N, Mitrov D, Esmerov I and Dovc P. 2014. Detection of recessive mutations (BLAD and CVM) in Holstein-Friesian cattle population in Republic of Macedonia. *Macedonian Veterinary Review* **37** (1): 61–68.

Agerholm J S, Andersen O, Almskou M B, Bendixen C, Arnbjerg J, Aamand G, Nielsen U S, Panitz F and Petersen A H. 2004. Evaluation of the inheritance of complex vertebral malformation syndrome by breeding studies. *Acta Veterinaria Scandinavica* **45** (3): 133–37.

Agerholm J S, Bendixen C, Andersen O and Ambjerg J. 2001. Complex vertebral malformation in Holstein calves. *Journal of Veterinary Diagnostic Investigation* **13**: 283–89.

Akyuz B, Ertugrul O and Agaoglu O K. 2010. Detection of bovine leukocyte adhesion deficiency (BLAD) allele in Holstein cows reared in Kayseri Vicinity. *Kafkas Üniversitesi Veteriner Fakültesi Dergisi* **16** (2): 519–21.

Akyuz B and Ertugrul O. 2008. Detection of deficiency of uridine monophosphate synthase (DUMP) in Holstein and native cattle in Turkey. *Veterinary Journal of Ankara University* **55**: 57–60.

Akyuz B, Sariozkan S and Bayram D. 2012. Factor XI mutation in normally fertile and repeat breeding Holstein cows in the Middle Anatolian region of Turkey: a financial approach. *Animal Production Science* **52** (11): 1042–45.

Anderson D C, Miller L J, Schmalstieg F C, Rothlein R and Springer T A. 1986. Contributions of the Mac-1 glycoprotein family to adherence-dependent granulocyte functions: Structure function assessments employing subunit specific monoclonal antibodies. *Journal of Immunology* **137** (1): 15–27.

Andrews A H, Fishwick J and Waters R J. 1996. Bovine leukocyte adhesion deficiency (BLAD) in a one year old Holstein Friesian bull- The first report in the United Kingdom. *British Veterinary Journal* **152**: 347– 51.

Asakai R, Davie E W and Chung D W. 1987 Organization of the gene for human factor XI. *Biochemistry* **26** (23): 7221–28.

Azad M S, Gupta I D, Verma A, Bohra V, Kumar S R and Kour K. 2011 Factor XI gene (plasma thromboplastin antecedent) deficiency in Karan Fries cattle. *Current Trends in Biotechnology and Pharmacy* **5** (1): 1060–63.

Berglund B, Persson A and Stalhammer H. 2004. Effects of complex vertebral malformation on fertility in Swedish Holstein cattle. *Acta Veterinaria Scandinavica* **45** (3): 161–65.

Biochard D, Coquereau J A and Amigues Y. 1995. Effect of bovine leukocyte adhesion deficiency genetic defect in Holstein cattle under farm condition. *46th Ann. Mett. Eur. Assoc. Anim. prod*., Prague.

Boujenane I and Ouhmama K. 2009. Prevalence of BLAD and CVM in Holstein dairy cattle introduced to Morocco. *Egyptian Journal of Animal Production* **46**(1): 19–26.

Brush P J, Anderson P H, Gunning R F, 1987. Identification of factor XI deficiency in Holstein Friesian cattle in Britain. *Veterinary Record* **121**(1): 14–17.

Chu Q, Dongxiao S, Ying Y, Yi Z and Yuan Z. 2008. Identification of complex vertebral malformation carriers in Chinese Holstein. *Journal of Veterinary Diagnostic Investigation* **20** (2): 228–30.

Chu Q, Zhang Y, Dong-Xiao S, Yung Y, and Ya-Chun W. 2010. Identification of the complex vertebral malformation gene in Chinese Holstein and its association with dairy performance traits. *Hereditas* **32** (7): 732–36.

Chung E R, Kim S K and Kim W T. 1997. Early diagnosis of BLAD and DUMPS inherited disease in Holstein dairy cattle using molecular genetic techniques, screening and frequency of BLAD gene. *Korean Journal of Dairy Science* **19** (4): 277–88.

Citek J, Rehout V, Hajkova J. and Pavkova J. 2006. Monitoring of the genetic health of cattle in the Czech Republic. *Veterinarni Medicina* **51** (6): 333–39.

Citek J, Rehout V, Schoffelova D and Hradecka E. 2008. Frequency of BLAD and CVM alleles in sires and elite heifers of Czech Holstein cattle. *Dtsch Tierarztl Wochenschr* **115** (12): 475–77.

Czarnik U and Kaminski S. 1997. Detection of intronic sequence in the bovine ITGB2 gene. *Journal of Animal Gen*etics **28** (4): 320–21.

Dennis J A, Heally P J, Beaduet A L and O'brien W F. 1989. Molecular definition of Bovine Argininosuccinate synthetase deficiency. *Proceedings of the National Academy of Sciences of the United States of America* **86** (20): 7947–51.

Duncan R B, Carrig C B, Agerholm J S and Bendixen C. 2001. Complex vertebral malformation in a Holstein calf: report of a case in the USA. *Journal of Veterinary Diagnostic Investigation* **13** (4): 333–36.

Esmaelizad M, Asadzadeh N, Molasalehi M and Hashemnejad K. 2002. Molecular characterization of CD18 gene and identification of BLAD carriers bulls in Iran. *Proceedings of the 7th World-Congress-on-Genetics-Applied-to-Livestock-Production*, Montpellier, France, August, Session **1**: 1–3.

Eydivandi C, Seyedabai H R and Amirinia C. 2011. Identification of BLAD, DUMPS and CVM deficiency in Khuzestan Holstein cattle population of Iran. *Global Veterinary* **6**: 519–24.

Fesus L, Anton I and Zsolnai A. 1999. Marker assisted selection in livestock. DUMPS, Weaver-diseases and Citrullinaemia in cattle population. *Allatt-es-Takarm* **48** (2): 193–203.

Gabor M, Martina M, Anna T, Zuzana R, Candrac J and Klara V. 2012. Detection of complex vertebral malformation carriers in Slovak Holstein cattle by high resolution melting analysis. *Acta Veterinaria* (Beograd) **62** (2–3): 239–48.

Gaur U, Sathe T G, Roy A, Sunkara P S S, Patel R K and Polisetti S V. 2012. Polymorphism in argininosuccinate synthase gene in Indian Holstein. *International Journal of Veterinary Science* **1** (3): 115–17.

Gaur U, Sathe T G, Roy A, Patel R K and Sunkara P S S. 2013.

First case of genetic polymorphism in Uridine monophosphate synthase gene in an Indian Holstein bull. *International Journal of Veterinary Science* **2** (1): 32–34.

Gentry P A and Black W D. 1980. Prevalence and inheritance of factor XI (plasma thromboplastin antecedent) deficiency in cattle. *Journal of Dairy Science* **63** (4): 616–20.

Gentry P A, Crane S, Lotz F. 1975. Factor XI (plasma thromboplastin antecedent) deficiency in cattle. *Canadian Veterinary Journal* **16** (6): 160–63.

Gentry P A and Downie H G. 1977. Blood coagulation. Swenson M J ed. *Duke's physiology of domestic animals*, 9th ed. Cornell University Press, Ithaca, New York.

Gentry P A, Overton K M and Robinson J L. 1996. Bovine factor XI deficiency. *Illinois Dairy Report* pp. 32–35.

Gentry P A and Ross M L. 1994. Coagulation factor XI deficiency in Holstein cattle: expression and distribution of factor XI activity. *Canadian Journal of Veterinary Research* **58** (4): 242–47.

Ghanem M E, Nakao T and Nishibori M. 2006. Deficiency of uridine monophosphate synthase (DUMPS) and X-chromosome deletion in fetal mummification in cattle. *Animal Reproduction Science* **91** (1): 45–54.

Ghanem M E, Nishibori M, Nakao T, Nakatani K, Akita M. 2005. Factor XI mutation in a Holstein cow with repeat breeding in Japan. *Journal of Veterinary Medical Science* **67** (7): 713–15.

Ghanem M E, Akita M, Suzuki T, Kasuga A and Nishibori M. 2008. Complex vertebral malformation in Holstein cows in Japan and its inheritance to crossbred F1 generation. *Animal Reproduction Science* **103** (3): 348–54.

Giger U, Boxer L A, Simpson P J, Lucchesi B R and Todd R F. 1987. Deficiency of leukocyte surface glycoproteins Mo1, LFA–1, and Leu M5 in a dog with recurrent bacterial infections: an animal model. *Journal of American Society of Hematology* **69** (6):1622–30.

Grupe S, Dietle G and Schwerin M. 1996. Population survey of Citrullinaemia on German Holsteins. *Livestock Production Science* **45** (1): 35–38.

Guillen E, Claudia A and Carlos B H. 1998. Mammalian Golgi apparatus UDP-N-acetyl glucosamine transporter: Molecular cloning by phenotypic correction of a yeast mutant. *Proceedings of the National Academy of Sciences of the United States of America* **95** (14): 7888–92.

Gurgul A, Rubioe D and Slota E. 2009. Identification of carriers of the mutation causing coagulation factor XI deficiency in Polish Holstein-Friesian cattle. *Journal of Applied Genetics* **50** (2): 149–52.

Harper P A, Healy P J, Dennis J A, O'Brien J J and Rayward D H. 1986. Citrullinaemia as a cause of death in neonatal Friesian calves. *Australian Veterinary Journal* **63** (11): 378–79.

Healy P J, Dennis J A, Camilleri L M, Robinson J L, Stell A L and Shanks R D. 1991. Bovine citrullinaemia traced to the sire of Linmack Kriss King. *Australian Veterinary Journal* **68** (4): 155.

Healy P J, Harper P A W and Dennis J A. 1990. Bovine citrullinaemia: a clinical, pathological, biochemical and genetic study. *Australian Veterinary Journal* **67** (7): 255–58.

Healy M H and Shanks R D. 1987. Performance of females heterozygous for deficiency of uridine monophosphate synthase. *Journal of Dairy Science* **70** (5): 945–51.

Huang Y C, Lin D Y, Tseng C Y, Chang H L, Huang Y C, Lin D Y, Tseng C Y and Chang H L. 2001. Comparison of milk production and quality of BLAD-carrier and normal Holstein-Friesian cows in Taiwan. *Journal of Taiwan Livestock Res*earch **34**: 271–78.

Janosa A, Baranyai B and Dohy J. 1999. Comparison of milk production of the progeny of BLAD-carrier and healthy Holstein bulls in Hungary. *Acta-Veterinaria-Hungarica* **47** (3): 283–89.

Jorgensen A S, Pedersen J and Thomsen P D. 1993. Bovine leukocyte adhesion deficiency in Danish Holstein-Friesian cattle. I. PCR screening and allele frequency estimation. *Acta Veterinaria Scandinavica* **34** (3): 231–36.

Kaminski S, Grzybowski G, Prusak B and Rusc A. 2005. No incidence of DUMPS carrier in Polish dairy cattle. *Journal of Applied Genetics* **46** (4): 395–97.

Kanae Y, Endoh D, Nagahata H and Hayashi M A. 2005. Method for detecting complex vertebral malformation in Holstein calves using polymerase chain reaction-primer introduced restriction analysis. *Journal of Veterinary Diagnostic Investi*gation **17** (3): 258–62.

Kehrli M E, Ackermann M R, Shuster D E, Maaten V D, Schmalstieg F C, Anderson D C and Hughes B J. 1990. Bovine leukocyte adhesion deficiency. ß$_2$ integrin deficiency in young Holstein cattle. *American Journal of Pathology* **140**: 1489–92.

Kehrli M E, Schmalstieg F C, Anderson D C, Maaten V D, Hughes B J, Ackermann M R, Wilhelmsen C L, Brown G B, Stevens M G and Whetstone C A. 1991. Molecular definition of the bovine granulocytopathy syndrome: Identification of deficiency of the Mac-1 (CD11b/ CD18) glycoprotein. *American Journal of Veterinary Research* **51**: 1826–36.

Khade A S, Doiphode A Y, Umrikar U D, Sawane M P and Pawar V D. 2014. Genotyping of the Holstein-Friesian crossbred cattle for *CD18* gene using PCR-RFLP. *Veterinary World* **7** (5): 360–62.

Kishimoto T K, Larson R S, Corbi A L, Dustin M L, Staunton D E and Springer T A. 1989. The leukocyte integrins. *Advances in Immunology* **46** (2): 149–82.

Kociba G D, Ratnoff O D, Loeb W F, Wall R L, Heider L E. 1969. Bovine Thromboplastin Antecedent (factor XI) deficiency. *Journal of Laboratory and Clinical Medicine* **74 (1)**: 37–41.

Konersmann Y, Wemheuer W and Brenig B. 2003. Origin, distribution and relevance of the CVM defect within the Holstein-Friesian population. *Zuchtungskunde* **75** (1): 9–15.

Kotikalapudi R, Patel R K, Sunkara P S S and Roy A. 2013. Detection of Silent Homozygous Polymorphism in Exon 4 of *SLC35A3*Gene in a Holstein Cattle Carrier for Complex Vertebral Malformation. *International Journal of Veterinary Science* **2** (2): 61–64.

Kucinskiene J and Miceikiene I. 2000. Bovine leukocyte adhesion deficiency (BLAD) - genetic basis and distribution in Lithuanian cattle population. *Latvia University of Agriculture* **162**: 13–16.

Kumar V and Sharma A. 2009. Bovine Leukocyte Adhesion Deficiency Syndrome (BLAD): A recessive disorder in Holstein Freisian cattle-A Review. *Agricultural Reviews* **30** (4): 293–300.

Kumar V, Chakravarty A K, Shivahre P R and Magotra A. 2013a. Effect of slc35a3 gene polymorphism on three month body weight of holstein crossbred calves. *Ruminant Science* **2** (2): 205–06.

Kumar V, Patil C S and Sharma R K. 2011c. Bovine factor XI deficiency: A recessive disorder in Holstein Freisian cattle-A Review. *Agricultural Reviews* **32** (3): 228–32.

Kumar V, Patil C S, Yathish H M and Sharma R K. 2013b. Effect

of CD18 gene polymorphism on three-month body weight of Holstein crossbred (Karan Fries) calves. *Indian Veterinary Journal* **90** (7): 93–95.

Kumar V**,** Singh R K and Sharma A. 2010. Deficiency of Uridine Monophosphate Synthase (DUMPS): A Recessive Disorder in Holstein Friesian Cattle- A Review. *Veterinary World* **3** (11): 523–25.

Kumar V, Yathish H M and Sharma A. 2011b. Single nucleotide polymorphism (snp) identification of cd18 gene in Indian Holstein crossbred cattle. *Indian Veterinary Journal* **88** (4): 40–41.

Kumar V, Sharma A, Yathish H M and Singh A. 2011a. Single nucleotide polymorphism (snp) identification of slc35a3 gene in Indian Holstein crossbred cattle. *Indian Veterinary Journal* **88** (11): 14–15.

Lee Y K, Chang K M, Nam I S, Chang W K, Tak J Y and Kim K N. 2002. Studies on the detections of congenital genetic disorder in Holstein proven and candidate bulls. *Journal of Animal Science and Technology* **44** (3): 279–88.

Li J, Wang H, Zhang Y, Hou M, Zhong J and Zhang Y. 2011. Identification of BLAD and citrullinemia carriers in Chinese Holstein cattle. *Animal Science Papers and Reports* **29** (1): 37–42.

Lin D, Huang Y, Chen J, Yang T, Shiao T and Chang H. 2001b. Investigation of citrullinaemia of dairy cattle in Taiwan. *Journal of Taiwan Livestock Research* **34** (4): 279–84.

Lin D Y, Huang Y C, Chang H L, Liaw R B, Lee S C, Chen J C, Wu S C and Wu M C. 2001a. DNA typing of inherited deficiency of Uridine Monophosphate Synthase in dairy cattle and beef cattle. *Journal of Chinese Society of Animal Science* **30** (1): 15–22.

Liptrap R M, Gentry P A, Ross M L, Cummings E. 1995. Preliminary findings of altered follicular activity in Holstein cows with coagulation factor XI deficiency. *Veterinary Research Communications* **19** (6): 463–71.

Llambi S, Guevara K, Rincon G, Zaffaroni R, Torres E, Barrera J, Arruga M V, Rodriguez V and Postiglioni A. 2003. Frequency of leukocyte adhesion deficiency in a population of Holstein-Friesian cattle in Uruguay**.** *Ars-Veterinaria* **19** (1): 52–56.

Mahdi M, Sharma A, Dubey P P, Kumar V, Mishra B and Joshi B K. 2010a. Identification of Complex Vertebral Malformation using Polymerase chain reaction primer introduced
restriction analysis in Karan Fries bulls. *Current Trend in Biotechnology and Pharmacy* **4** (4): 850–54.

Mahdi M, Sharma A, Dubey P P, Singh A, Tantia M S, Mishra B, Kumar V and Joshi B K. 2010b. PCR based identification of Bovine Leukocyte Adhesion Deficiency Syndrome (BLAD) carriers in Karan Fries bulls. *Indian Journal of Animal Sciences* **80** (5): 433–35.

Marron B M, Robinson J L, Gentry P A and Beever J E. 2004. Identification of a mutation associated with factor XI deficiency in Holstein cattle. *Animal Genetics* **35** (6): 454–56.

Mateusen B, Last T, Vercauteren G, Mommens G and Kruif A. 2004. Complex vertebral malformation in a Belgian Holstein Friesian calf. *Vlaams-Diergeneeskundig-Tijdschrift* **73** (5): 341–43.

Mei W H, Bin L J, Hai H M, Hong Z X, Hao L W and Feng Z J. 2009. Development and application of PCR-RFLP for detecting bovine citrullinemia and deficiency of uridine monophosphate synthase. *Chinese Journal of Veterinary Science* **29** (5): 661–64.

Meydan H, Yildiz M A, Ozdil F, Gedik Y and Ozbeyaz C. 2009. Identification of factor XI deficiency in Holstein cattle in Turkey. *Acta Veterinaria Scandinavica* **51** (5):1–4.

Meydan H, Yildiz M A and Agerholm J S. 2010. Screening for bovine leukocyte adhesion deficiency, deficiency of uridine monophosphate synthase, complex vertebral malformation, bovine citrullinaemia and factor XI deficiency in Holstein cows reared in Turkey, Acta Veterinaria Scandinavica **52** (1): 56.

Muraleedharan P, Khoda V, Sven G, Mukhopadhyaya P N, Manfred S and Mehta H K. 1999. Incidence of hereditary citrullinemia and bovine leukocyte adhesion deficiency syndrome in Indian dairy cattle (*Bos taurus*, *Bos indicus*) and buffalo (*Bos bubalis*) population. *Archiv Tierzucht Dummerstorf* **42** (4): 347–52.

Nagahata H, Miura T, Tagaki K, Ohtake M, Noda H, Yasuda T and Nioka K. 1997. Prevalence and allele frequency estimation of bovine leukocyte adhesion deficiency (BLAD) in Holstein-Friesian cattle in Japan. *Journal of Veterinary Medical Science* **59** (4): 233–38.

Nagahata H, Noda H, Takahashi K, Kurosawa T and Sonoda M. 1987. A suspected case of neutrophil dysfunction in a Holstein heifer. *Japanese Journal of Veterinary Science* **49** (6): 1165–67.

Nagahata H, Oota H, Nitanai A, Oikawa S, Higuchi H, Nakade T, Kurosawa T, Morita M and Ogawa H. 2002. Complex vertebral malformation in a stillborn Holstein calf in Japan. *Journal of Veterinary Medical Science* **64** (12): 1107–12.

Nassiry M R, Norouzy A, Eftekharishahrody F, Javadmanesh A and Alishad, M. 2005. Investigation of two recessive disorders in breeder bulls of Abbas Abad animal breeding center. *Iranian Journal of Biotech*nology **3** (2): 125–28.

Nielsen U S, Aamand G P, Andersen O, Bendixen C, Nielsen V H and Agerholm J S. 2003. Effects of complex vertebral malformation on fertility traits in Holstein cattle. *Livestock Production Science* **79** (2): 233–38.

Norouzy A, Nassiry M R, Eftekharishahrody F, Javadmanesh A, Mohammad Abadi M R and Sulimova G E. 2005. Identification of bovine leukocyte adhesion deficiency (BLAD) carriers in Holstein and Brown Swiss AI bulls in Iran. *Russian Journal of Genetics* **41**(12): 1697–701.

Oner Y, Keskin A and Elmasi C. 2010. Identification of BLAD, DUMPS, Citrullinaemia and FXI deficiency in Holstein cattle in Turkey. *Asian Journal* of *Animal* and *Veterinary Advances* **5** (1): 60–65.

Patel R K, Kalpesh J S, Jenabhai B C, Krishna M S and Sambasiva Rao K R S. 2007b. Factor XI deficiency in Indian *Bos taurus*, *Bos indicus*, *Bos taurus* × *Bos indicus* crossbreds and *Bubalus bubalis*. *Genetics and Molecular Biology* **30** (3): 580–83.

Patel R K, Singh K M, Soni K J, Chauhan J B and Sambasiva Rao K R S. 2006. Investigation on occurrence of citrullinaemia and DUMPS in Indian Holstein cattle. *Journal of Applied Genetics* **47** (3): 239–42.

Patel R K, Singh K M, Soni K J, Chauhan J B and Sambasiva Rao K R S. 2007a. Low incidence of bovine leukocyte adhesion deficiency (BLAD) carriers in Indian cattle and buffalo breeds. *Journal of Applied Genetics* **48** (2): 153–55.

Poli M A, Dewey R, Semorile L, Lozano M E, Albarino C G, Romanowski V and Grau O. 1996. PCR screening for carriers of bovine leukocyte adhesion deficiency (BLAD) and Uridine monophosphate synthase (DUMPS) in Argentine Holstein cattle. *Zentralbl Veterinarmed A* **43** (3): 163–68.

Powell R L, Norman H D and Cowan C M. 1996. Relationship of

bovine leukocyte adhesion deficiency with genetic merit for performance traits. *Dairy Science* **79** (5): 895–99.

Rahimi G, Javaremi A N and Olek K. 2006. Genotyping BLAD, DUMPS, ê-CSN loci in Holstein young bulls of the National Animal Breeding Centre of Iran. *Pakistan Journal of Biological Sciences* **9** (7): 1389–92.

Revell S. 2001. Complex vertebral malformation in a Holstein calf in the UK. *Veterinary Research* **149**: 659–60.

Rezaee A R, Nassiry M R, Valizadeh R, Tahmoorespour M, Javadmanesh A, Zarei A and Janati H. 2008. Study of Complex Vertebral Malformation Disorder in Iranian Holstein Bulls. *World Journal of Zoology* **3** (2): 36–39.

Ribeiro L A, Baron E E, Martinez M L and Coutinho L L. 2000. PCR screening and allele frequency estimation of bovine leukocyte adhesion deficiency in Holstein and Gir cattle in Brazil. *Genetics* and *Molecular Biology* **23** (4): 831–34.

Robinson J L, Burns J L, Magura C E and Shanks R D. 1993. Low incidence of citrullinaemia carriers among dairy cattle of the United States. *Journal of Dairy Science* **76** (3): 853–58.

Rosenthal R L, Dreskin O H, Rosenthal N. 1953. New hemophilia-like disease caused by deficiency of a third plasma thromboplastin factor. *Proceedings of the Society for Experimental Biology and Medicine* **82** (1): 171–74.

Roy A, Kotikalapudi R, Patel R K, Anantaneni R and Katragadda S. 2012. New Cases of Bovine Leukocyte Adhesion Deficiency (BLAD) Carriers in Indian Holstein Cattle. *International Journal of Veterinary Science* **1**(2): 80–82.

Rusc A and Kaminski S. 2007. Prevalence of complex vertebral malformation carriers among Polish Holstein-Friesian bulls. *Journal of Applied genetics* **48** (3): 247–52.

Rusc A, Hering D, Puckowska P, Barcewicz M and Kaminski S. 2013. Screening of Polish Holstein-Friesian bulls towards eradication of Complex Vertebral Malformation (CVM) carriers. *Polish Journal of Veterinary Sciences* **16** (3): 579–81.

Sahin E, Taki K, Askin G and Sonar M. 2013. Identification of bovine leukocyte adhesion deficiency (BLAD) and bovine citrullinaemia (BC) alleles in Holstein cows reared in Antalya region. *Journal of Applied Animal Research* **41** (1): 56–60.

Schilcher F, Hotter H, Tammen I and Schuh M. 1995. Bovine leukocyte adhesion deficiency among Holstein-Frie-sian cattle in Austria. *Wien Tieraerztl Monsehr* **82**: 207–12.

Schwenger B, Schober S and Simon D. 1993. DUMPS cattle carry a point mutation in the Uridine Monophosphate synthase gene. *Genomics* **16** (1): 241–44.

Shanks R D and Robinson J. 1990. Deficiency of uridine monophosphate synthase among Holstein cattle. *Cornell Veterinarian* **80** (2): 119–22.

Shanks R D, Bragg D S and Robinson J L. 1987. Deficiency of uridine monophosphate synthase in Holstein cattle: inheritance and body measurements. *Journal of Animal Science* **64** (3): 695–700.

Sharma R K, Suchdeva G K, Tantia M S and Kumar V. 2013b. Argininosuccinate Synthetase (ASS) gene polymorphism causing bovine citrullinemia in Karan Fries cattle. *Indian Veterinary Journal* **90** (1): 69–71.

Sharma R K, Suchdeva G K, Tantia M S, Kumar V and Patil C S. 2013a. Uridine Mono Phosphate Synthase (UMPS) gene polymorphism causing DUMPS in Karan Fries Cattle. *Indian Veterinary Journal* **90** (1): 75–77.

Shuster D E, Kehrli M E, Ackermann M R. and Gil-bert R O. 1992. Identification and prevalence of a genetic defect that causes leukocyte adhesion deficiency in Holstein cattle. *Proceedings of the National Academy of Sciences of the United States of America* **89**: 9225–29.

Springer T A, Thompson W S, Miller L J, Schrnalstieg F C and Anderson D C. 1984. Inherited deficiency of the Mac-I, LFA-I, p150, 95 glycoprotein family and its molecular basis. *Journal of Experimental Medicine* **160**: 1901–18.

Tainturier D, Grobet L, Brouwers B, Bruyas J F, Fieni F, Battut I, Lecoanet J, Douart A, Breyton I and Duclos P. 1995. Observations on three cases of bovine leukocyte adhesion deficiency (BLAD). *Revue-de-Medecine-Veterinaire* **146** (3): 189–93.

Takahashi K, Miyagawa K, Abe S, Kurosawa T, Sonoda M, Nakade T, Nagahata H, Noda H, Chihaya Y and Isogai E. 1987. Bovine granulocytopathy syndrome of Hol-stein Friesian calves and heifers. *Japanese Journal* of *Veterinary Science* **49** (4): 733–36.

Thomsen B, Horn P, Panitz F, Bendixen E, Petersen A H, Holm L E, Nielsen V H, Agerholm J S, Arnbjerg J and Bendixen C. 2006. A missense mutation in the bovine SLC35A3 gene, encoding a UDP-N-acetylglucosamine transporter, causes complex vertebral malformation. *Genome Research* **16** (1): 97–105.

Wang C, Tong Q, Hu X Z, Yang L G and Xhong X Q. 2011. Identification of complex vertebral malformation carriers in Holstein cattle in south China. *Genetics and Molecular Research **10(4)***: 2443–48.

Wang S, Hao H, Zhao X, Zhu H and Du W. 2012. A rapid mismatch polymerase chain reaction assay to detect carriers of complex vertebral malformation in Holstein cattle. *Journal of Veterinary Diagnostic Investigation **24 (3)***: 568–71.

Wouda W, Borst G H, Vos J H, Peperkamp N H, Visser I J and Zeeuven A A. 2001. A newly recognized hereditary syndrome in Holstein-Friesian calves characterized by vertebral malformations, cervicotruncal dwarfism, arthrogryphosis and cardiac defects. *Proceedings of 19th Meeting of the European Society of Veterinary Pathathology, Thessaloniki* 168.

Wouda W, Visser I J, Borst G H, Vos J H, Zeeuwen A A and Peperkamp N H. 2000. Developmental anomalies in aborted and stillborn calves in The Netherlands. *Veterinary Record* **147** (21): 612.

Yathish H M, Sharma A, Kumar V, Jain A, Chakraborty D, Singh A and Tantia M S. 2011. Genetic polymorphism of SLC35A3 gene in Karan fries young bulls. *Indian Journal of Animal Sciences* **81** (9): 951–53.

Yathish H M, Sharma A, Kumar V, Jain A, Chakraborty D, Singh A, Tantia M S and Joshi B K. 2010. Genetic Polymorphism of CD18 gene in Karan Fries Young bull Calves using PCR-RFLP Analysis. *Current Trends in Biotechnology and Pharmacy* **4** (4): 900–07.

Zhang K, Wang Z and Wang Q. 2010. Detecting factor XI deficiency in Holstein cattle using PCR analysis. *Agricultural Science and Technology* **11** (5): 109–11.

Zhang Y, Fan X, Sun D, Wang Y, Yu Y, Xie Y, Zhang X and Zhang Y. 2012. A novel method for rapid and reliable detection of complex vertebral malformation and bovine leukocyte adhesion deficiency in Holstein cattle. *Journal of Animal Science and Biotechnology* **3** (1): 24.