BOVINE FACTOR XI DEFICIENCY: A RECESSIVE DISORDER IN HOLSTEIN FRIESIAN CATTLE- A REVIEW

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ABSTRACT
Bovine Factor XI Deficiency is one of the most important recessive hereditary disorder of Holstein cattle. It is characterized by prolonged bleeding, anemia, greater prevalence of repeat breeding, or even lower resistance to pneumonia, mastitis and metritis resulting in reduced reproductive performance and increased susceptibility to disease. The molecular basis of this coagulopathy has been recognized in Holstein cattle as a 76-bp insertion in the coding region of the FXI gene. This disorder has an adverse impact on reproductive traits and udder health in cattle. The only way to avoid economic losses is through an early detection of carriers. The use of PCR based molecular technologies promises quick detection of carriers enables their culling and thus controlling and preventing the spread of FXI deficiency in the population.

Keywords: Bovine Factor XI Deficiency, Coagulopathy, FXI gene, Holstein cattle.

There are more than 5000 autosomal recessive genetic diseases in humans. A small number of such diseases are also identified in animals and many of them are equivalent to human diseases. In cattle, the autosomal recessive genetic diseases are breed-specific. Some of them are Holstein breed specific, which include Bovine Factor XI Deficiency Syndrome (Brush et al. 1987), Complex Vertebral Malformation (Revell, 2001), Bovine Leukocyte Adhesion Deficiency Syndrome (Kerhli et al. 1990) and Deficiency of Uridine Monophosphate Synthase (Robinson et al. 1993). Inherited disorders affect all kinds of farm animals. Functional and physiological defects arising from inherited disorders have negative impact on health and productivity of farm animals. Autosomal recessive disorders lead to economic loss in the dairy cattle industry due to difficulty in detection of carrier individuals. Increased use of artificial insemination and worldwide use of service bull lead to widespread of this kind of disorders via carriers. 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 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).

A rare hereditary disorder, known as factor XI (FXI) deficiency, has been recognized in humans (Rosenthal et al. 1953) and cattle (Kociba et al. 1969; Gentry et al. 1975). FXI deficiency is an autosomal recessive disorder, with partial deficiency of FXI coagulant activity in heterozygotes and considerable deficiency in homozygotes (Gentry and Ross 1994). In cattle, FXI-deficient animals may be asymptomatic or display several symptoms like

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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). A biochemical test based on activated partial thromboplastin time (APTT) makes it possible to diagnose deficient animals, but fails to provide reliable results in the case of abnormal gene carriers (Gentry and Ross 1986). 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-colored colostrum. Blood in the milk led to the identification of the condition in a British dairy herd. Additionally, FXI deficiency causes 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 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. Pedigree analysis indicate that FXI deficiency is an autosomal recessive disorder like BLAD, DUMPS and CVM. Accordingly, carriers (heterozygous) of the defective gene are outwardly normal, while affected animals (homozygous) have a mild hemophilia-like disorder; 25 per cent of the offspring of a carrier bull and a carrier cow will be affected with a FXI deficiency. Carrier cattle exhibit varying symptoms and degrees of reduced FXI activity.

Current testing methods measure the activated partial thromboplastin time (APTT) to monitor FXI activity. Although affected animals with FXI deficiency are relatively easy to classify, carriers of the disorder are often difficult to distinguish from normal individuals because of the overlap of activity ranges. To effectively control the spread of recessive defects such as BLAD, DUMPS, CVM and FXI deficiency it is important to accurately identify animals that may appear clinically normal, but carry the mutant allele. 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).

FXI deficiency may also affect reproduction traits and udder health in cattle. Because reproduction problems and udder inflammation may generate definite pecuniary losses in commercial farms. Under a study in Poland preliminary screening of the Polish Holstein cattle population in search of exon 12 insertion was done. In total, 140 cattle were genotyped for the FXI gene mutation. A total of 103 samples were obtained from randomly selected cows originating from various herds located throughout Poland. Additional 28 samples were taken from cows with repeat breeding, and another 9 from cows with recurrent mastitis from the Experimental Farm Chorzelów Ltd. and commercial herds located in the Wielkopolska province. The repeat breeding cows were clinically healthy and did not conceive at least 3 inseminations. The cattle with recurrent mastitis were tested positive for this disease at least twice in the past. Mastitis was confirmed by commercial tests.

**History of bovine Factor XI Deficiency**

An inherited deficiency of Factor XI results in bleeding disorder that has been documented in humans, dogs, and cattle. The bovine form of the disease was first discovered in Holstein cattle in Ohio in 1969. It was later observed among Holstein-Friesians in Canada, England, and Australia. Like DUMPS and BLAD, it is inherited in an autosomal recessive manner. Accordingly, carriers (heterozygotes) of the defective gene are outwardly normal, while affected animals (homozygotes) have a mild hemophilia-like disorder; 25 per cent of
offspring of mating a carrier bull to a carrier cow will be affected with Factor XI deficiency. In 1975, a herd of Factor XI 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 per cent of normal biological activity of plasma Factor XI, with most having less than 1 per cent. Carrier animals have from 20 to 60 per cent of normal levels, with a mean value of 38 ± 10 per cent. 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”.

Molecular basis of bovine Factor XI Deficiency

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)28AAATAATG(A)26G] followed by a duplicated region of the normal coding sequence [GAAATAATAATCT], introduces a premature stop codon, which impairs the synthesis of functional protein.

Genome organization of cattle FXI Gene

FXI gene is located on chromosome number 4 in human and on chromosome number 8 in mouse. FXI gene is present on chromosome number 27 in cattle (NCBI RefSeq: NC_007328.3). It is 19150 bp in length from 17607721 to 17626871 nucleotide having 15 exons and 14 introns.

Protein structure and molecular biology of FXI

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. This protein is present in plasma as zymogen (Fig 1), which is a unique plasma coagulation enzyme because it exists as a homodimer consisting of two identical polypeptide chain linked by disulfide bonds. During activation of the plasma factor XI, an internal peptide bond is cleaved by factor XII in each of the two chains, resulting in activated factor XI. This activated plasma factor XI triggers the middle phase
of the intrinsic pathway of blood coagulation by activating factor IX.

**Status of Bovine Factor XI Deficiency in India**

Mukhopadhaya et al., (2006) carried on PCR based DNA analysis for screening of animals for FXI deficiency in various dairy cattle and buffalo breeds in Gujarat. Their findings have been given in Table 1.

Similarly, another study was carried out by Patel et al., (2007) at NDDB, Anand, India for screening of breeding bulls of various indigenous and crossbred cattle and buffaloes (Table 2).

In a study carried by Azad (2010) at NDRI, Karnal, India for screening of 253 Sahiwal cattle and 200 Karan Fries cattle for Bovine FXI deficiency, none of the animal was found affected or carrier.

**DNA test for identifying different genotypes:**

In order to identify FXI genotypes DNA extractions were obtained from the fresh blood of the cows. Amplicons of FXI exon 12 were obtained by Polymerase Chain Reaction (PCR) and analyzed by 2% agarose gel electrophoresis stained with ethidium bromide. Additionally, all cows were confirmed by DNA sequencing to determine whether or not there was a mutant allele.

**Checklist for managing bovine Factor XI Deficiency in a herd**

i) A system should be set up for accurate recording of sire and maternal grandsire ID for all cows in the herd.

2) List or spreadsheet file should be made showing the FXI deficiency status of the sire and maternal grandsire of each cow in the herd.

3) Selection index should be used such as Lifetime Net Merit, to identify the group of AI sires likely to be used in the herd during the next three months.

4) FXI deficiency carrier bulls should be avoided for using on any cow whose sire or maternal grandsire is a carrier.

5) Modern genetic tools help us to identify undesirable genes and to eliminate them in a rapid and efficient manner and should be utilized.

**CONCLUSION**

With the wide use of artificial insemination (AI) and international trading of semen and breeding bulls, these genetic diseases have spread to a large population, as carrier animals of the diseases appear normal. Mahdipour et al, (2010), Kumar et al, (2010, 2011a) and Yathish et al, (2011) examined Karan Fries animals for BLAD and they found that per cent of carriers were 7.31, 21.82 and 3.64 respectively. Mahdipour et al, (2011) and Kumar et al, (2011b) examined Karan Fries animals for CVM and they found that per cent of carriers were 23.07 and 76.28 per cent respectively. In India, where Holstein Friesian (HF) bulls and their semen are extensively used for crossbreeding programmes with indigenous cattle, it has become necessary to screen all HF and HF crossbreds, especially AI bulls, to minimize the risk of spreading these diseases among future bulls or bull mothers.

**REFERENCES**


