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GENETIC DISORDERS THAT CAUSE STILLBIRTH AND ABORTION IN CATTLE

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ABSTRACT

SUMMARY Genetic disorder is an illness caused by inborn abnormalities in gene or chromosomes, which are quite rare. It causes abortion and still birth. The word abortion is usually used to define the termination of a pregnancy, and still birth occurs anytime a calf dies from 260 days of gestation up until 24 hours post calving. Genetic disorders in cattle are mostly caused by autosomal recessively inherited gene. These autosomal recessively inherited genes are formed due to deletion or insertion of mutant genes. The genetic diseases in dairy and beef cattle are tissue specific viz; Skeletal, Central Nervous System and Blood. Genetic disorders that cause abortion and still birth in cattle includes skeletal disorders such as: Achondroplasia, Mulu Foot (syndactylism), Complex Vertebral Malformation, Arachnomelia, Osteogenesis Imperfecta, Arthrogryposis Multiplex and Brachyspina syndrome; central nervous system disorders such as: spinal dysmyelination and spinal muscular atrophy; blood tissue disorders of, Bovine Leukocyte Adhesion Deficiency. It causes loss of calf, lower fertility of the dam at the next breeding, longer calving to conception interval, and a tendency for milk production to be decreased. Therefore, in order to reduce this economic lose the DNA testing is currently available for some of the genetic disease; however, it is necessary to develop it for all the genetic diseases so that breeding sires can be effectively screened for undesirable alleles and culled to avoid further propagation in breeding population.

KEY WORDS : Abortion, Cattle, Stillbirth, Genetic disorders.

1.INTRODUCTION

Abortion is one of the major causes of economic loss in the dairy and beef cattle industry. This includes costs associated with loss of milk production, feed, replacement costs and labor (Hovingh, 2009). The word abortion is usually used to define the termination of a pregnancy; however, a distinction should be made between early embryonic death, abortions and stillbirths. Early embryonic death is pregnancy loss before the organogenesis (the formation of the calf's internal organs) is complete, which usually occurs around day 42 of gestation. Pregnancy loss between days 42 and 260 of gestation is considered a true abortion. Stillbirth occurs anytime a calf dies from 260 days of gestation up until 24 hours post calving. There are multiple causes of abortions and still birth in cattle. These are infectious agents such as bacteria, viral agents (Bovine Viral Diarrhea and Infectious Bovine Rhinotracheitis), protozoa, fungi and mycotoxins and non- infectious agents such as genetic abnormalities; heat stress; hormonal abnormalities, nutritional deficiencies, trauma (Hernandez *et al., 1999)*.

Perhaps the most frequent cause is infectious agents such as bacteria. The major bacterial agents that have been implicated in bovine abortion during mid- to late-gestation are *Brucella* spp., *Chlamydia* spp., *Salmonella* spp., *Campylobacter* spp., *Salmonella spp., Listeria monocytogenes* and *Coxiella burnetii* Bovine (Dondo et al., 2011). Brucellosis was distributed worldwide, and its importance is related not only to the economic losses in animal production but also to a significant risk for human health. The abortion generally occurs from 6 to 9 months of gestation. It is frequently followed by fetal membrane retention and endometritis, which may be the cause of infertility in subsequent pregnancies (Mohammed *et al.,* 2009).

A genetic disorder is an illness caused by inborn abnormalities in genes or chromosomes, which are quite uncommon and affect one animal in every several thousands or millions. A genetic disease may or may not be a heritable disease as some genetic disorders are passed down from the parent's genes, but others are always or almost always caused by new mutations or changes to the DNA. Genetic abnormalities contribute to poor animal performance, structural unsoundness, semi-lethal disease, or lethal disease (Gholap *et al*., 2014a). The most common inheritance pattern of genetic disease is as a simple recessive trait. A few inherited defects are known to be caused by genes with incomplete dominance and a few are caused by two or more sets of genes (Schalles and Leipold, 2012a).

Around 200 different genetic defects have been identified in cattle. Some of these are: Bulldog (achondroplasia), Mule Foot (syndactylism), Bovine Leukocyte Adhesion Deficiency (BLAD), Complex Vertebral Malformation (CVM), Brachyspina Syndrome, Prolonged Gestation, Hairlees, Osteopetrosis Weaver Syndrome, Spinal Dysmyelination, Spinal Muscular Atrophy, Imperfect Skin, Deficiency of Uridine Monophosphate Synthase (DUMPD), Osteogenesis Imperfect, Short Spinal Lethal, Epitheliogenesis Imperfecta, X-Linked Anhydrotic Ectodermal Dysplacia, Anapthlomos and Micropthalmos. Congenital Cataract, Optic Nerve Colobomas, Arachnomelia, Arthrogryposis Multiplex, Congenital Contractural Arachnodactyly etc. From these the major common ones that cause abortion and stillbirth in cattle are: Bulldog (achondroplasia), Mule Foot (syndactylism), Bovine Leukocyte Adhesion Deficiency, Complex Vertebral Malformation, Spinal Dsymyelination, Spinal Muscular Atrophy, Arachnomelia, Osteogenesis Imperfect, Brachyspina Syndrome and Arthrogryposis Multiplex (Zabek and Rys. 1998). From the skeletal CVM affects fetal development, being a cause of frequent abortions and stillbirths. This characterized in growth retardation and bilateral flexure of the carpal and metacarpophalangeal joints along with rotation of the digits.

Therefore, the objective of the current seminar is:

- To point out major genetic disorders that cause abortion and stillbirth in cattle.

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2. GENETIC DISORDERS THAT CAUSE STILL BIRTH AND ABORTION IN CATTLE

A genetic disease is an illness caused by inborn abnormalities in genes or chromosomes, which are quite uncommon and affect one animal in every several thousands or millions. The genetic diseases in dairy and beef cattle are tissue specific like; skeletal, central nervous system, blood and skin. A genetic disease may or may not be a heritable disease as some genetic disorders are passed down from the parent's genes, but others are always or almost always caused by new mutations or changes to the DNA. 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 (Gholap *et al*., 2014a).

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. A few inherited defects are known to be caused by genes with incomplete dominance and a few are caused by two or more sets of genes (Schalles and Leipold, 2012b). Common genetic defects that cause abortion and still birth in cattle are complex vertebral malformation, chondrodysplasia, spinal dysmyelination, spinal muscular atrophy, arachnomelia, osteogenesis imperfect, arthrogryposis multiplex, brachyspina syndrome, syndactylism and bovine leukocyte adhesion deficiency. Other defects, which we do not know about, yet, might be present and new defects will certainly turn up in future (Steinbock *et al*., 2003).

2.1Skeletal Disorders that Cause Stillbirth and Abortion in Cattle

2.1.1. Arachnomelia

Arachnomelia is a lethal inherited malformation mainly of the limbs, vertebral column and skull in cattle, and inherited as a monogenic autosomal recessive trait with complete penetrance, which poses a severe impairment to farmers and breeders (Weppert *et a*l., 2008). Affected calves are usually still birth with a spidery appearance and an abnormally shaped skull. The bones of the limbs are prolonged with marked thinning of the diaphyses that fracture easily in the course of forced birth assistance. Additional dysmorphic features are variable, e.g. Defects of the vertebral column and sometimes cardiac malformations, (Gentile and Testoni, 2004).

The main cause of this defect is due to SUOX gene (BTA5) mutation encoding molybdohemoprotein sulphite oxidase. The causal mutation was a single base insertion c.363–364insG in the fourth exon of the sulfite oxidase (*SUOX*) gene leading to premature stop (p.Ala124GlyfsStop42) and deletion c.1224-1225delC (frame shift p.His24fsStop73) which led to a frame-shift and a predicted premature stop codon (Testoni *et al.,* 2010). Clinically Spider leg affected calves are usually stillborn or die during birth, although some live for a few hours. Facial deformities (short lower jaw and concave rounding of the dorsal profile of the maxilla), legs longer and thinner than normal, severe angular deformities in the distal part of the hind legs (marked bilateral hyperextension of the fetlocks (Semmer *et al.,* 2011**).** Joints may be hyper mobile or frozen (requiring fetal dissection in the uterus to aid in birth). Fragile bones. Spontaneous fractures during birth could result in injuries to the dam's uterus and genital passage. Small and underdeveloped muscles. Short, crooked or taut, over stretched tendons. Short skull with dent in the frontal bone. Short lower jaw (Chavaz, 1987).

2.1.2 Brachyspina syndrome

Brachyspina syndrome (BS), a genetic abnormality in the Holstein cattle breed that causes either early-term abortion (most common) or stillborn calves (rare) when an individual is homozygous recessive for the lethal gene, was first observed in Denmark in 2006. Later, additional cases were reported in the Netherlands, Italy, Germany,and Canada (Agerholm *et al.,*2006). The main cause of Brachyspina syndrome is mutation of (*FANCI*) gene. Mutation occurs due to a 3.3-kb deletion in the bovine (*FANCI*) gene. The deletion removed exons 25–27 of the 37 exons composing *FANCI*, and led to a frame-shift substituting of the 451 carboxy-terminal amino acids with a 26 residue long illegitimate peptide (Charlier *et al*., 2012a).

The cases were characterized morphologically by severely reduced body weight despite a normal or slightly prolonged gestation period, obvious shortening of the spine, long and slender limbs, inferior brachygnathism and internal organ malformation, such as renal and gonadal dysplasia. At the same time, the defect is responsible for some fertility problems, such as a high proportion of abortions and long calving interval (Charlier *et al.,* 2012b). A large proportion of cases probably die during embryonic or early fetal development (similar to CVM (Thomsen *et al*., 2006a), thus causing reduced fertility and unpredictable economic losses to the breeders.

2.1.3 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*., 2004). 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 Arthrogryposis (Agerholm *et al.,* 2001).

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) genes (Kanae *et al*., 2005). The bovine SLC35A3 to be the first nucleotide-sugar transportation regulating gene also responsible in the formation of vertebrae and ribs (*Christian et al., 2005a)*. Defective calves have this mutation in both alleles, thus proving the autosomal recessive nature of the disorder. The gene SLC35A3 codes for a nucleotide-sugar transporter in which the base mutation is reflected in an amino acid substitution at position 180 (valine to phenylalanine), thus inhibiting the function of the transporter. The nucleotide-sugar transporter plays an essential role in mechanisms controlling the formation of vertebrae from the unsegmented paraxial mesoderm. Consequently, the defective transporter molecule leads to vertebral malformations (Thomsen *et al*., 2006b).

A CVM affected calf typically has an abnormally short neck and crooked pasterns. Other malformations associated with CVM are malformations or fusing of vertebrae, scoliosis, contraction and crookedness of distal joints, and abnormal shape of head (*Christian et al., 2005b)*. It also affects fetal development, being a cause of frequent abortions and stillbirths. As many as 88 percent of homozygous, CVM affected foetuses are spontaneously aborted within 260 days from the insemination. A normal bovine pregnancy lasts 280 days. Only 4-5 percent of CVM affected fetuses are calved alive. These calves however are nonviable (*Gert et al., 2002)*. Diagnose based on just visual examination of a calf may be difficult due to the wide variety in the expression of anomalies, and a definite diagnosis requires DNA testing **(***Frank et al., 2005)*.

Treatment is usually unsuccessful. It is recommended to cull the CVM carriers gradually for economical and breeding reasons (Chu *et al*., 2010).

2.1.4 Chondrodysplasia

Chondrodysplasia (bulldog calves, achondroplasia, disproportionate dwarfism) is a designation used for a heterogeneous group of congenital skeletal malformations characterized by diminished endochondral osteogenesis. The morphological appearance shows wide variation, but the main feature of all cases is reduced length of bones with an endochondral growth pattern. Some types of chondrodysplasia are associated with foetal death and abortion. Others cause semilethal conditions and several types produce viable but short-legged calves. Chondrodysplasia has been reported in many cattle breeds and at least nine different inherited types have been recorded (Wageningen, 2000).

It is primarily caused by defects in aggrecan (*ACAN*) genes that

regulate normal chondrogenesis and cartilage development, resulting in abnormal shape and structure of the skeleton. ACAN gene encoding the protein aggrecan is known as chondroitin sulfate proteoglycan 1. This protein is an integral part of the extracellular matrix in the cartilaginous tissue. The defect occurs two different mutations. These are *BD1 mutation*: It is due to mutation of a 4 bp insertion c.2266-2267insGGCA in exon 11 introducing amino acid position 756 and pre mature termination codon at position 914 as compared to the normal aggrecan product of 2337 amino acid, BD2 mutation: it is due to point mutation of c.198>Tn exon 1. The transition is predicted to introduce a new ATG start codon 199 bp of the normal start codon and hence 91 amino acids protein bearing are not resemblance to the aggrecan protein due to the frame shift of nature of the new start codon (Cavanagh *et al*., 2007).

Affected calves are aborted, mostly in the 6th to 8th month of gestation. The cows may have hydramnion with associated oedema of the foetal placenta. The affected fetuses are characterized by severe disproportionate dwarfism with prominent shortening of the spine and a compact body. There is a severe dysplasia of the splanchnocranium with palatoschisis and doming of the neurocranium, sometimes associated with hydrocephalus. Extreme tetramelic shortening of the limbs is seen. Longitudinal sawing of the bones reveals short diaphyses with prominent cartilaginous epiphyses. An abdominal defect with eventration of abdominal organs may be present (Harper *et al*., 1998a). The epiphyses are characterized histologically by hyaline cartilage. Distinct epiphyseal growth plates are lacking. Hypertrophied chondrocytes and chondrocyte alignment are irregular and almost absent. The diaphyses consist of dense, cancellous bone and compact bone (Harper *et al.,* 1998b).

2.1.5 Syndactylism

Syndactylism (mule foot) is a congenital malformation of the distal parts of one or more limbs characterized by complete or partial fusion or non-division of the functional digits. Syndactylism develops due to fusion or non-divisions of the foetal anlage of digits III and IV. The main cause of defect is due to the deletion and insertion of c.4863-4864delCGinsAT (p.Asn1621Lys; p.G1622C) and point mutation c.4940>T (p.Pro1647Lys) (Duchesne et al., 2006a).

Typical cases of syndactylism are externally recognized by the presence of a single hoof-like structure instead of the normally paired claws. Sometimes dorsal midline groove may be present. The morphological variation reflects the underlying skeletal malformation. Thus, cases observed which shows narrow interdigital cleft and fusion of only the most proximal part of the claw capsules. This type of cases may remain unrecognized unless the digits are carefully inspected. Some extra morphological abnormalities, such as synostosis, may develop in other parts of the distal appendicular skeleton of affected limbs, for example, in metacarpal/ metatarsal bones and carpal/tarsal bones. Concomitant adaptive changes are found in the muscles, tendons, nerves and vascular supply of the distal limb and abortion (Baker *et al*., 1987).

Clinically this disorder observed by the presence of a single hoof-like structure instead of the normally paired claws. A dorsal midline groove may be present. The phonotypical structural variation shows the underlying skeletal malformation. The fusion or non-division of the two developed digits of the foot is observed **(**Duchesne et al., 2006b).

2.1.6 Osteogenesis imperfect

Osteogenesis imperfecta is a lethal heritable disorder of connective tissue characterized by varying degrees of congenital bone fragility and defects of the dense connective tissue in tendons, ligaments and skin. Dysplastic dentin and abnormally thin (and therefore blue) sclera are seen in many OI syndromes (Denholm and Cole, 1983). The generalized fragility of bone and dentin and the joint laxity in OI is due to structural defects in collagen fibrils comprised of Type 1 collagen. Type 1 collagen is the most abundant structural protein found in the extracellular matrix of vertebrate bones and dense connective tissues. It constitutes an important component of bone, tendons, ligaments, skin and teeth. The protein is a heterotrimer made of two a1 (I) and one a2 (I) chains, which are coded by the COL1A1 and COL1A2 genes, respectively. The a-chains consist mainly of repeated tripeptide motifs, which all start with a glycine molecule. This construction is essential for correct formation of the collagen helix structure. It assembles into fibrils forming the structural scaffold of bone, dentin, tendon, skin and other connective tissues (Han, *2008*).

In general terms, the causal mutations in dominantly transmitted OI syndromes are likely to be found in the COL1A genes and those in the recessive syndromes more likely to be in genes that encode proteins involved in post-translational modification of the type 1 procollagen propeptides or regulation of type 1 collagen fibrillogenesis. Defects of collagen fibrillogenesis can be detected ultra-structurally in the tendon and bones of OI affected calves. Reduced mean tendon collagen fibril diameters and failure to develop the normal bimodal distribution of collagen fibril diameters in tendon during post-natal growth are typical ultra-structural findings in OI, accompanied by dilation of the rough endoplasmic reticular cisternae of the tendon fibroblasts with abnormal fibrillar secretory product (Denholm, 1985).

The majority of known COL1a1 affect protein-coding regions, typically within the triple-helix domain that is composed of a repeating amino acid sequence with glycine, the smallest of the amino acids, in every third position and primarily separated by proline residues (Wada et al. 2006). This repetition is crucial, as it enables the triple-helix domain to wind into its compact structure in type I collagen. As such, the most phenotypically severe OI type II often result from substitutions of these glycine, whereas less severe phenotypes (e.g., OI type I) often result from alterations of the length of the triple-helix domain, which is normally encoded by 43 of 51 exons within the >17-kb *COL1a1* locus (Rauch *et al*., 2010). OI affected calves present with poor growth rates, spontaneous multiple fractures, congenital or post-natal bone deformation (from healed fractures), generalized joint laxity, dentinogenesis imperfecta and blue sclera **(**Huq *et al*., 2005). Biochemical changes have been found in Australian and North American cases, but the molecular basis has not been identified for any bovine cases (Citek *et al*., 2009).

2.2 Genetic Neurological Disorders that Causes Still Birth and Abortion in Cattle

2.2.1. Arthrogryposis multiplex

Arthrogryposis multiplex (curly calf syndrome) is a rare neurogenetic disorder of cattle worldwide (Windsor *et al*., 2011). This disease is generally found in Angus cattle. This defect caused due to autosomal recessive gene. Exact cause of the disease is due to the deletion of a section of DNA (at least 38,000 bp) that encompasses two different genes. The mutation results in no protein being produced (loss of function mutation) (Whitlock 2010). Clinical signs associated with arthrogryposis include multiple deformities including cleft palate, misshapen spine, tendon contractures, cardiac deformities, bilaterally tibia (twisted rear leg with anchylosed joints), stillbirth, severe scoliosis and torticollis, severe fixed contractures of all limbs, mainly distal, and lateral deviation of the face in some cases. Sometime abdominal hernia and cranial defect (cranioschisis with meningocele) are found (Huffel *et al.,* 1986).

2.2.2 Spinal muscular atrophy

Spinal muscular atrophy is a neurodegenerative disease characterized by severe loss of motor neurons. Degeneration and loss of motor neurons cause progressive weakness and neurogenic muscular atrophy. (Krebs *et al.,* 2007a). Muscular Atrophy is a progressive lethal autosomal recessive disease. It is reported mainly in Spinal advanced backcrosses between American Brown Swiss and European Brown Cattle abut it is also observed in Holstein-

Friesian calves (Joerg.*et al.,* 2005). The disease is caused by a mutation in a gene which produces 3-ketodihydrosphingosine (KDS) reductase activity, which plays an important role in the biosynthesis of glycosphingolipids. Loss of this enzyme activity results in neuronal degeneration and progressive degenerative neuronal atrophy (Krebs, 2006).

SMA occurs in a familiar pattern consistent with autosomal recessive inheritance. Recent molecular studies have strongly indicated that a missense mutation in the gene FVT1, coding for 3-ketodihydrosphingosine reductase, is the cause of SMA. This enzyme has housekeeping functions related to sphingolipid metabolism and is crucial for neuronal development and function. The missense mutation lowers the enzymatic activity of 3 ketodihydrosphingosine reductase to a level insufficient for survival of ventral horn motor neurons, which are selectively affected because of their high metabolic rate and extensive transport processes along the axons (Krebs *et al*., 2007b).

The clinical signs are dominated by progressive muscular weakness leading to recumbency and finally death. Muscular atrophy develops and is especially conspicuous in the hind limbs. Most calves suffer from bronchopneumonia, possibly as a sequel to aspiration, and lesions associated with recumbency, including decubital lesions and chemically induced dermatitis on the ventral abdomen in male calves (Vestweber *et al*., 1993). Clinically affected calves, especially heifers, present with hind leg weakness and reluctance to stand from 2 weeks of age. Severe muscular atrophy is evident on palpation of hind limbs. Most calves tend to die within 2 weeks of birth. Symptoms include: Loss of balance in rear legs, Difficulty in standing, Calves lie with front legs outstretched, wasting away of muscle mass, Eventual inability to stand and Labored breathing (Leipold, 1989).

Diagnosis is based on presenting clinical signs augmented with tissue samples of hind limb muscles which show motor neuron swelling, chromatolysis and loss of neurons in the ventral horn, axonal swelling in the spinal cord, and accumulation of neurofilaments in affected neurons. There is no treatment for affected calves which invariably die (Hamidi, 1989).

2.2.3 Spinal dysmyelination

Spinal dysmyelination is a lethal congenital neurological disorder of crossbred American Brow n Swiss calves. This disorder was introduced into the Danish Red Dairy breed because of crossbreeding with American Brown Swiss. Affected animals show congenital recumbency, often in a lateral position with opisthotonos and bilateral symmetric extension of the limbs. The head and front limbs have a normal position, but the hind limbs are still extended if the calves are placed in the sternal position. Efforts of limb movement and support are absent when calves are raised manually. Reflexes are either nor mal or increased. The calves are alert until they become debilitated due to infections (Lutz, 1996).

The disease is apparent as the calf is born. The SPAST gene (BTA11), encoding the spastin protein is the affected gene of this disease. The defect is due to the missense mutation c.560G>A (p.Arg560Glu). Sometime gross lesions are absent at necropsy, but some calves may show muscular atrophy, and the cervical and thoracic spinal cord segments might seem decreased in size on transverse section. Main clinical findings are lateral recumbency with slight opisthotonos and spastic extension of the limbs. Occasionally, swollen axons and a few neurons with central chromatolysis are seen in the brain stem. Variable degrees of denervation atrophy may be present in the skeletal musculature (Hafner *et al*., 1993a)

Gross lesions are generally absent at necropsy, but some calves may have muscular atrophy, and the cervical and thoracic spinal cord segments might seem decreased in size on transverse section. Characteristic histological lesions are present in the gracile funiculus, dorsolateral spinocerebellar tract and the sulcomarginal tract, and consist of bilateral symmetric hypodemyelination (dysmyelination) with astrocytosis, oligodendrocyte necrosis and axonal degeneration. These lesions are recognizable until lumbar segment 1, where the characteristic dysmyelination of the gracile funiculus disappears. The tract-associated lesions are no longer recognisable posterior to lumbar segment 4. Occasionally, a few neurons with central chromatolysis and swollen axons are seen in the brain stem. Variable degrees of denervation atrophy may be present in the skeletal musculature (Hafner *et al*., 1993b).

As the lesions reflect an impaired oligodendrocyte function and maturation a candidate gene should be associated with these functions (Hafner *et al*., 1993c). SDM shows its affects immediately upon birth of the calf. The calf cannot stand at all after birth, and it will have spastic movement in its rear legs although they seem normal otherwise. SDM is also believed to be passed on as a genetic recessive. This means that two carriers must be mated for the condition to occur and then it will occur only once in every four offspring. SDM symptoms generally appear at birth symptoms include inability to stand immediately after birth, vertebral column twists, large blood vessel aneurysms, Spastic rear legs and Calf otherwise alert. There is no cure for this condition (Agerholm *et al.,* 1994).

2.3 Blood Tissue Disorders That Cause Stillbirth and Abortion in Cattle

2.3.1 Bovine Leukocyte Adhesion Deficiency

Bovine leukocyte adhesion deficiency (BLAD) is a rare autosomal recessive lethal genetic disease of Holstein and Friesian cattle. Affected calves suffer from frequent infections, which either fail to respond to or recur after conventional treatment. BLAD is caused by a point mutation in the gene encoding bovine CD18, producing a substitution of a guanine for adenine and of an aspartic acid to glycine at amino acid 128 (D128G) (Nasreen *et al.,* 2009). The disease is characterized by recurrent pneumonia, ulcerative and granulomatous stomatitis, enteritis, periodontitis, delayed wound healing, neutrophilia and early death. Affected calves normally die before reaching sexual maturity (Sun *et al*., 2011).

In calves born with leukocyte adhesion deficiency, infections by Salmonella spp can be fatal. This disease has been commonly reported in Holstein and Friesian calves (Meydan, 2010a). The resulting decline in use of semen from carrier bulls led to a decrease in the occurrence of the condition. The extensive use of artificial insemination in dairy cattle allows this strategy to have a rapid impact (Meydan *et al.,* 2010b).

2.4 Diagnosis, Treatment and Control of Genetic Disorders in Cattle

Genetic abnormalities in the fetus that result in abortion are not very frequently diagnosed, and these usually occur as an individual cow problem rather than as a herd outbreak. These abnormalities, which may not cause a change in the outward appearance of the fetus, may result in abortion because of the growing fetus' inability to develop properly in the uterus. Genetic abnormalities may also cause obvious physical changes in the fetus, just as other infectious agents (*John*, *2009*).

Diagnostic tests generally are required to further support a genetic disorder in a diseased animal. Radiology and other imaging techniques may reveal skeletal and CNS malformations or cardiac anomalies, and ophthalmologic examination may further define an inherited eye disease, although some are not recognized before several years of age. The laboratories' approach is to detect the failing system or to determine the specific protein or gene defect. The molecular defect has been identified for several hereditary diseases, and thus DNA screening tests have been developed. These tests are mutation specific and can therefore only be used in animals suspected to have the exact same gene defect. The DNA segment of interest is amplified with appropriate primers and polymerase chain reaction (PCR). The mutant and/or normal allele are identified directly by DNA sequencing or size differences on a gel in case of deletions or insertions or after restriction enzyme

digestion for point mutations. These tests are generally simple, robust, and accurate as long as appropriate techniques and controls are used (Giger, 2000a).

Much more important than the treatment of hereditary disorders is the control of these traits in breeding programs. Thus, in order to reduce the frequency or eliminate altogether a genetic defect, the further spread of the mutant gene has to be prevented in a family or entire breed. It is obvious that affected animals of any genetic disease should not be used for breeding. This approach is simple and effectively eliminates disorders with a dominant trait. For recessively inherited disorders, however, the elimination of affected animals is not sufficient to markedly reduce the prevalence of a defect within a breed. Although it may be safest not to breed any related animals of affected animals, this practice may, because of inbreeding and narrow gene pools in some breeds, eliminate all breeders in an entire kennel or cattery, and may severely reduce the genetic diversity of a breed (Giger, 2000b).

2.5 Economic Importance of Genetic Disorders

Furthermore, increasing average herd sizes, which most likely gives less time for supervision of calving, might result in a larger proportion of difficult calving being recorded as stillbirths. The large number of stillborn calves is both an ethical and an economic problem. The economic problem comprises loss of the calf, lower fertility of the dam at the next breeding, longer calving to conception interval, and a tendency for milk production to be decreased (Chassagne *et al.*1999). For example, CVM causes extensive foetal mortality as analyses of population-based breeding results have demonstrated a significant lack of calves born near term. Studies of Danish Holsteins have shown that the extent of foetal mortality prior to gestation day 260 is approximately 77% *(*Nielsen *et al., 2003)*.

3. CONCLUSION AND RECOMMENDATIONS

Genetic disorders are of great concern in cattle breeding as the breeding systems and the extensive use of genetically related sires predispose to increased frequency of recessively inherited disease genes in the population and subsequently the occurrence of diseased animals. Inherited disorders may in this way contribute significantly to the extent of calf diseases and mortality as elite sires may produce hundreds of thousands of progenies. Furthermore, high numbers of defective animals may be reached due to international trade with semen, which links national cattle populations together genetically. The genetic disease causes the heavy losses because of poor animal performance; structural unsoundness reduces the production and reproductive potential of the animal. If genetic disease remains undetected, then it will get propagated from generation to generation continuously which will increase the occurrence of the undesirable genes in the breeding population affecting negatively on per animal productivity. Therefore, based on the above conclusion the following recommendations are forwarded:

- It is necessity to have awareness about the genetic diseases of cattle.
- Selected breeding sires must be screen for genetic diseases in order to avoid an unnecessary spread within the population

- **ABBREVIATIONS**
- (*ACAN*) aggrecan
- (*FANCI*) Fanconi anemi complementation-group 1
- A adinaine
- Arg arginine
- BD1 Bromodomain 1
- BD2 Bromodomain 2
- bp Base pair
- BTA *Bos taurus* autosomes
- C cytosine
- C. chain
- COL1A1 collagen type 1alpha1
- COL1A2 collagen type 1alpha2
- CVM The complex vertebral malformation
- del deletion
- FVT1 follicular variant translocation protein 1
- G guanine
- Glu glutamine
- ins insertion
- insG insertion of guanine
- OI Osteogenesis imperfecta
- p. protein
- SDM spinal dysmyelination
- SLC35A3 solute carrier family 35 member A3
- *SUOX* sulfite oxidase
- T tiamine
- Ala alanine
- Gly glycine
- fs frameshif
- DNA deoxyribonuclic acid
- PCR polymarase chain reaction

Conflicts of Interest

The authors declare that they have no conflicts of interest.

Data Availability: The data used to support the findings of this study are available from the corresponding author upon request.

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