Wayamba Journal of Animal Science – ISSN: 2012-578X; P483 - P 485, 2012
First Submitted October 31, 2012; Number 1351665777

COMPLEX VERTEBRAL MALFORMATION (CVM) IN HOLSTEIN

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Complex vertebral malformation (CVM) is an autosomal recessively inherited disorder in Holstein cattle worldwide, which usually onsets during fetal development, leading to abortion of fetuses or perinatal death, and vertebral anomalies. Disease symptoms have not been observed in carriers of CVM. Detailed clinical characterization of CVM demonstrated a composite phenotype with axial skeletal deformities such as hemivertebrae, misshaped vertebrae, ankylosis of mainly the cervico-thoracic vertebrae, scoliosis, and symmetric arthrogryposis of the lower limb joints, craniofacial dysmorphism, as well as cardiac anomalies (Agerholm et al. 2004a, 2004b; Nielsen et al. 2003). The syndrome was first discovered in the Danish Holstein population in 1999 (Agerholm et al. 2001), but shortly thereafter reported in the United States (Duncan et al. 2001, Holstein Association, USA, 2004), the United Kingdom (Revell 2001), the Netherlands (Wouda et al. 2000), and in Japan (Nagahata et al. 2002), Germany (Konersmann et al. 2003), Sweden (Berglund et al. 2004), Denmark (Thomsen et al. 2006), India (Mahdipour et al. 2010). The percentage of CVM carrier reported worldwide is very high. Japan reported highest incidence 32.50% of CVM (Nagahata et al (2002) and Germany reported lowest 13.20% (Konersmann et al., 2003), whereas India reported 23.07% (Mahdipor et al, 2010).

Genealogical records traced the origin of the disease-causing allele to a common ancestral bull, Carlin-M Ivanhoe Bell, which has been used in dairy cattle breeding worldwide for two decades due to the superior lactation performance of his daughters. Coincidently Carlin-M Ivanhoe Bell was a carrier for two genetic diseases, CVM and Bovine leukocyte adhesion deficiency (BLAD). The BLAD and CVM genes are located on chromosomes 1 (Shuster et al. 1992) and chromosome 3 (Thomsen et al. 2006) respectively. Carlin-M Ivanhoe Bell was a carrier for two genetic diseases, CVM and Bovine leukocyte adhesion deficiency (BLAD). The BLAD and CVM genes are located in different chromosomes. When the sire (father) of Carlin-M Ivanhoe Bell, a bull named Pennstate Ivanhoe Star, was tested he was found to be a carrier of both CVM and BLAD. Carlin-M Ivanhoe Bell's grandsire Osborndale Ivanhoe, however, carried only BLAD. Scientists therefore believe that the mutation responsible for CVM occurred either in Pennstate Ivanhoe Star (Sire), or somewhere in his maternal family.

Biochemical aspect of CVM

The Impaired protein molecules, a UDP-N-acetylglucosamine transporters or Golgi UDP-GlcNAc transporters (alternative name) in the Golgi apparatus membrane, causes CVM. These transporter proteins transport *Uridine diphosphate N-acetylglucosamine or UDP-GlcNAc* (a nucleotide sugar and a coenzyme in metabolism), from cytosol/Cytoplasm (synthesis site) into the Golgi lumen before these can be substrates for the glycosylation of proteins, lipids, and proteoglycans. The *UDP-GlcNAc* (a nucleotide sugar and a coenzyme in metabolism) plays an important role in the structure of the cytoskeleton,

Molecular aspect of CVM

The molecular cause of CVM is a substitution of guanine by thymine (G→T) in a solute carrier family 35 member 3 gene (*SLC35A3*), encoding a UDP-N-acetylglucosamine transporter. The gene is located on bovine chromosome BTA3 (Thomsen et al. 2006). This mutation results in the substitution of Valine by

Phenylalanine (V180F) at position 180, impairing transporter membrane protein.

Precisely

Bovine Solute carrier family 35 member 3 gene (*SLC35A3*) located on BTA3

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Encodes for Uridine diphosphate *N*-acetylglucosamine transporter or UDP-GlcNAc, cell membrane permeable protein.

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Transporter protein transfer *Uridine diphosphate N-acetylglucosamine* or *UDP-GlcNAc* (nucleotide sugar and a coenzyme in metabolism) from Cystol (synthesis site) to Golgi lumen before these can be substrates for the glycosylation of proteins, lipids, and proteoglycans.

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UDP-GlcNAc (nucleotide sugar) plays an important role in the structure of the cytoskeleton

Molecular Diagnosis of CVM

As it is caused by single point mutation in *SLC35A3* gene with no restriction site, it may be analysed by using single-stranded conformation polymorphism (PCR-SSCP) (Orita et al. 1989). The alternate method is Primer Introduced Restriction Analysis (PCR-PIRA) which creates *Pst* I restriction site in wild gene during PCR (Kanae et al., 2005). Once restriction site is created, restriction fragment length polymorphism (RFLP) can be performed.

CONCLUSION

In cattle, the most pressing problem in the genetics of health at present is the recessive and lethal Complex Vertebral Malformation (CVM), and other genetic diseases in the Holstein population. Hence, all HF and their crosses should be screened at the early age along with other genetic disorders; BLAD, Citrullinaemia, DUMPS, FXI etc., and culled if found carrier to prevent risk of spreading such disorders.

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