Black Sea Journal of Agriculture
doi: 10.47115/bsagriculture.1603011

Open Access Journal
e-ISSN: 2618 - 6578

Review
Volume 8 - Issue 3 : 427-430 / May 2025

BOVINE GENETIC DISEASES - OLD SYNDROMES IN A NEW PERSPECTIVE

Jørgen Steen AGERHOLM[1]*

[1]*University of Copenhagen, Faculty of Health and Medical Sciences, Department of Veterinary Clinical Sciences, 2630, Taastrup, Denmark*

Abstract: Congenital malformations have always fascinated humans but it was not until recently that deeper knowledge on their causes have become more evident. The development within genomic analysis has until now resolved the molecular cause of almost 200 bovine genetic diseases. However, the cause of certain well-known congenital syndromes in cattle have remained unexplained. The Danish Bovine Genetic Disease Program was in its current form established in 1989 and many genetic diseases have been investigated. Lately, we have focused on some well-known congenital disorders: schistosoma reflexum, congenital syndromic Chiari-like malformation and the bulldog calf syndrome. Genetic analyses of such cases sampled as part of the bovine genetic disease surveillance in Denmark have confirmed their genetic etiology. Investigations into a fourth congenital syndrome, perosomus elumbis, are underway.

Keywords: Schistosoma reflexum, Spina bifida, Bulldog calf, Chiari malformation; Perosomus elumbis

***Corresponding author:** University of Copenhagen, Faculty of Health and Medical Sciences, Department of Veterinary Clinical Sciences, 2630, Taastrup, Denmark
E mail: jager@sund.ku.dk (J. S. AGERHOLM)
Jørgen S AGERHOLM https://orcid.org/0000-0003-1653-4552

Received: December 17, 2024
Accepted: January 23, 2025
Published: May 15, 2025

Cite as: Agerholm JS. 2025. Bovine genetic diseases - Old syndromes in a new perspective. BSJ Agri, 8(3): 427-430.

1. Introduction

Congenital malformations have throughout history always puzzled and fascinated people. In the Middle Ages, occurrence of malformed animals was considered supernatural, while during the Enlightenment (17th and 18th centuries), scientists tried to understand why congenital malformations occurred. However, it was only after Gregor Johann Mendel's (1822-1884) description of the laws of heredity that a deeper understanding of the importance of genetics for the development of malformed fetuses grew. Still there was a long way to go to understand the causes themselves. In the 1920s, the first hereditary malformations in cattle were identified based on the Mendelian laws, but the actual understanding of why malformations develop had to await the breakthrough in genetic technology that enabled the identification of mutations, and thereby an understanding of the molecular mechanisms that lead to abnormal fetal development.

The number of recognized genetic disorders in cattle has raised steadily since Lerner in 1944 published a list of 44 lethal or sub-lethal conditions in cattle until today (July 26, 2024), where 270 diseases with Mendelian inheritance are recognized and of which at least one likely causal variant is known for 189 (OMIA, 2024).

The development within genetic technology is growing fast, which has made identification of mutations and other chromosomal abnormalities easier, more rapid and less costly.

Surveillance for genetic diseases in cattle was in Denmark formally established in 1989, which has led to the recognition and eradication of several genetic conditions. During recent years, we have tried to solve the riddle of bovine congenital syndromes that have been known for many decades or even longer. Here, an introduction to our recent research on a number of these classical bovine syndromes is given.

2. Schistosoma Reflexum

Schistosoma reflexum (SR) is a congenital syndrome characterized by dorsal retroflexion of the spine. The spine will thereby get an almost U-shaped form with the consequence that the hindlimbs point in the direction of the head. The retroflexion of the spine, hinders ventral midline closure of the fetal body cavities and therefore their contents (intestines, etc.) protrude (Figure 1).

A fetus affected by SR is born alive at the end of a normal length gestation period, but die immediately due to impaired respiration. SR is associated with dystocia and affected fetuses must be released by cesarean section or fetotomy unless the size of the fetus/the size of the maternal birth canal allow assisted vaginal delivering.

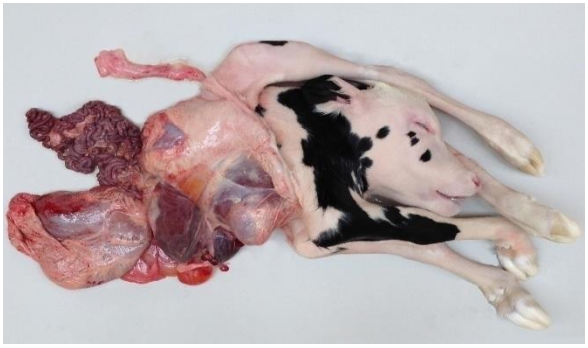

Figure 1. A typical case of schistosoma reflexum in a Holstein calf.

SR occurs sporadically in cattle but its etiology has not been known. Recessive inheritance has been proposed as some Holstein cases were genetically related (Citek, 2012), but a genetic cause has not been proven. Genetic relationship in cattle breeding as evidence of inheritance should be interpreted with caution as some breeding lines have been widely used and therefore some sires may be present in the pedigree of most cattle of certain breeds.

We investigated DNA of 23 SR cases, mostly Holsteins (n=20) and when available, also their parents. Evidence of recessive inheritance was not found, but we were able to detected frameshift and missense variants in 12 cases. These genes belonged to the class of haploinsufficient loss-of-function genes, are involved in embryonic and pre-weaning lethality or are known to be associated with severe malformation syndromes in other species and therefore considered causal for development of SR. Study details have been published in Jacinto et al. (2024a).

3. Congenital Syndromic Chiari-Like Malformation

Congenital syndromic Chiari-like malformation (CSCM) is a sporadically occurring malformation that is often associated with dystocia (breech presentation). The most striking lesion is an almost bilateral symmetric arthrogryposis of the hindlimbs associated with hypo-/dysplasia of the associated muscles.

Figure 2. A case of congenital syndromic Chiari-like malformation. Notice the bilateral symmetric hindlimb arthrogryposis, lumbar lordosis and the flattened neurocranium. Reprinted from Jacinto et al. (2024b).

In many cases, a closer examination reveals a hairless skin lesion in the dorsal midline of the lumbar spine. This represents spina bifida, i.e. a lesion where the vertebral arch is not complete so the spinal cord is exposed. The spina bifida is sometimes covered by skin (a so-called spina bifida occulta).

The rostral aspect of neurocranium is often flattened. This causes compression of the developing brain and due to insufficient space, parts of the brain is dislocated caudally and some parts even protrude through the foramen magnum into the vertebral canal, a so-called Chiari type II like malformation.

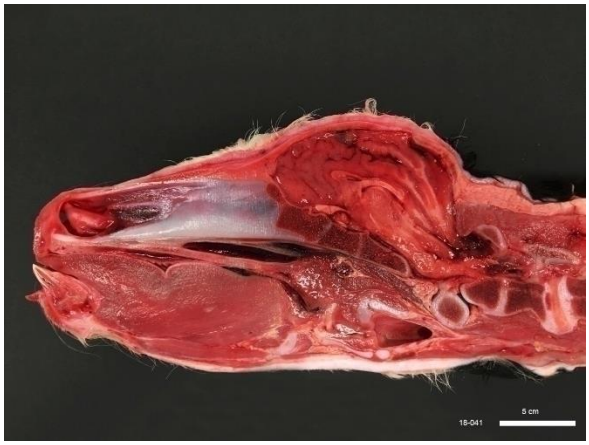

Figure 3. Chiari type II-like malformation. Notice that the occipital lobes are dislocated towards the foramen magnum and the cerebellum and parts of the brain stem protrudes into the vertebral canal.

We performed a genomic analysis of 14 cases of CSCM (mainly Holsteins) and when available, also their parents and discovered that CSCM is due to extensive genetic heterogeneity, including both possible recessive alleles and dominant acting *de novo* mutations. The two recessive missense variants were identified in the genes *SHC4* and *WDR45B*, respectively. Analysis of 1209 sires included in the 1000 Bull Genomes Project (Hayes and Daetwyler, 2019) revealed the presence of carriers of both variants. The *SHC4* variant may originate from the sire Wapa Arlinda Conductor (born 1970) or one of his parents, while the *WDR45B* variant could be traced to the sire Mascol (born 2000). Partial monosomy of chromosome 2 was identified in two other cases. Study details have been published in Jacinto et al. (2024b).

4. Perosomus Elumbis

Perosomus elumbis (PE) is a congenital syndrome characterized by lack of development of the lumbar, sacral and coccygeal spinal segments (Figure 4 and 5). The spine and the spinal cord end near the thoraco-lumbar junction and the caudal part of the body therefore consists of a hypoplastic pelvis, hypoplastic hindlimbs with arthrogryposis, and an abdominal wall sac-like structure that encloses the abdominal organs (Agerholm et al., 2014).

This syndrome occurs sporadically and is associated with dystocia as the fetus is often in breech presentation.

We have recorded several cases in the Danish surveillance program for bovine genetic diseases. Some have occurred sporadically, but we have also encountered a cluster of cases after a Belgian Blue sire used for crossbreeding. Multiple cases after a single sire indicates that a dominant paternal germline mutation is the cause of PE in this particular family and that the sire is mosaic for a causal mutation, but as found for SR and CSCM, PE can probably develop due to a range of genetic scenarios.

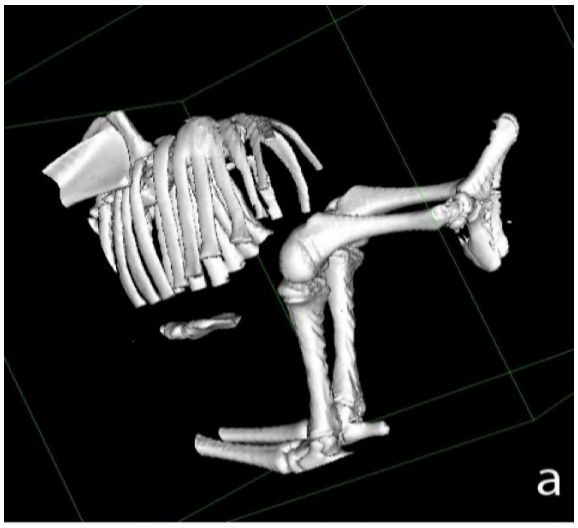

Figure 4. Surface rendered computed tomography image of perosomus elumbis. The lack of spinal development caudal to the thorax is visualized. Reprinted from Agerholm et al. (2014).

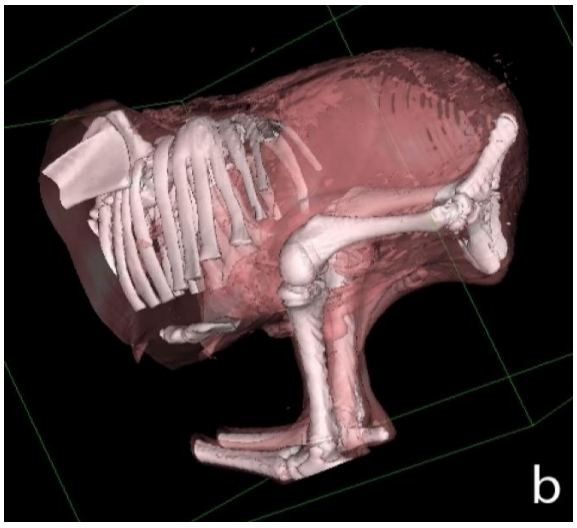

Figure 5. Surface rendered computed tomography image of perosomus elumbis The skin surface of the calf is visualized. Reprinted from Agerholm et al. (2014).

5. Bulldog Calf Syndrome

The bulldog calf syndrome (BCS) or bovine congenital generalized chondrodysplasia was the first hereditary disorder to be reported in cattle (Seligmann, 1904) and was therefore given the number A1 on Lerner's list from 1944. BCS was originally reported in the Dexter breed, but BCS has turned out to consist of a very heterogeneous group of skeletal malformations that have disturbed endochondral ossification in common (Agerholm, 2007). The phenotype and mode of inheritance varies across different cases.

The "prototype" of BCS has dysplasia of the viscerocranium, a doomed neurocranium, a short compact body and short compact limbs (Figure 6). The tongue is often protruding because of the short viscerocranium and eventration of parts of the abdominal organs is a common finding, which is due to the short body that reduces the size of the body cavities.

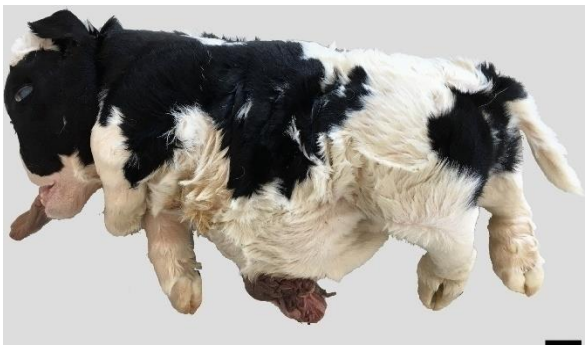

Figure 6. Typical case of the bulldog calf syndrome. Holstein fetus. Reprinted from Jacinto et al. (2020).

Genetic analyses of BCS cases have in many cases identified a causal mutation in the *collagen type II alpha 1 chain* gene (*COL2A1*) as reviewed by Jacinto et al. (2020). Some cases have occurred in clusters related to a single phenotypically normal sire, who had then been mosaic for the causal mutation and carried the dominant mutation for BCS at a certain level in his spermatozoa (1-21%) (Daetwyler et al. 2014; Bourneuf et al. 2017). Other cases have been due to a *de novo* mutation occurring in the developing embryo. Study details have been published in Jacinto et al. (2020).

6. Conclusions

Identifying the cause of a congenital syndrome in cattle is important to prevent spread of genetic disorders, to increase the breeders' economy by reducing loss of offspring and future breeding animals, and to reduce the critical animal welfare issues related to birth of defective offspring. However, as many important congenital syndromes share a common morphology (disease prototype), detailed genetic investigations are needed to differentiate between inherited and *de novo* mutations that have occurred in the developing embryo. While the former may require implementation of breeding restrictions, lethal mutations occurring in the developing embryo are not transmitted to the next generation.

Author Contributions

The percentages of the author' contributions are presented below. The author reviewed and approved the final version of the manuscript.

	J.S.A.
C	100
D	100
S	100
L	100
W	100
CR	100
SR	100

C= concept, D= design, S= supervision, L= literature search, W= writing, CR= critical review, SR= submission and revision.

Conflict of Interest

The author declared that there is no conflict of interest.

Ethical Consideration

Ethics committee approval was not required for this study because there was no study on animals or humans.

Acknowledgments

This article was presented as an oral presentation at the VIII. International Congress on Domestic Animal Breeding, Genetics and Husbandry - 2024 (ICABGEH-24) Antalya, TÜRKİYE, September 23 - 25, 2026. Professor Cord Drögemüller and his research group at the University of Bern is greatly acknowledge for the genetic analyses.

References

Agerholm JS. 2007. Inherited disorders in Danish cattle. APMIS, 122(115): 1-76.

Agerholm JS, Holm W, Schmidt M, Hyttel P, Fredholm M, McEvoy FJ. 2014. Perosomus elumbis in Danish Holstein cattle. BMC Vet Res, 10: 227.

Bourneuf E, Otz P, Pausch H, Jagannathan V, Michot P, Grohs C, Piton G, Ammermüller S, Deloche M-C, Fritz S, Leclerc H, Péchoux C, Boukadiri A, Hozé C, Saintilan R, Créchet F, Mosca M, Segelke D, Guillaume F, Bouet S, Baur A, Vasilescu A, Genestout L, Thomas A, Allais-Bonnet A, Rocha D, Colle M-A, Klopp C, Esquerré D, Wurmser C, Flisikowski K, Schwarzenbacher H, Burgstaller J, Brügmann M, Dietschi E, Rudolph N, Freick M, Barbey S, Fayolle G, Danchin-Burge C, Schibler L, Bed'Hom B, Hayes BJ, Daetwyler HD, Fries R, Boichard D, Pin D, Drögemüller C, Capitan A. 2017. Rapid discovery of de novo deleterious mutations in cattle enhances the value of livestock as model species. Sci Rep, 7: 11466.

Citek C. 2012. Pedigree analysis of Czech Holstein calves with schistosoma reflexum Acta Vet Scand, 54: 22.

Daetwyler HD, Capitan A, Pausch H, Stothard P, van Binsbergen R, Brøndum RF, Liao X, Djari A, Rodriguez SC, Grohs C, Esquerré D, Bouchez O, Rossignol MN, Klopp C, Rocha D, Fritz S, Eggen A, Bowman PJ, Coote D, Chamberlain AJ, Anderson C, VanTassell CP, Hulsegge I, Goddard ME, Guldbrandtsen B, Lund MS, Veerkamp RF, Boichard DA, Fries R, Hayes BJ. 2014. Whole-genome sequencing of 234 bulls facilitates mapping of monogenic and complex traits in cattle. Nat Genet, 46: 858-865.

Hayes BJ, Daetwyler HD. 2019. 1000 Bull Genomes Project to map simple and complex genetic traits in cattle: applications and outcomes. Ann Rev Anim Biosci, 7: 89-102.

Jacinto JGP, Häfliger IM, Letko A, Drögemüller C, Agerholm JS. 2020. A large deletion in the *COL2A1* gene expands the spectrum of pathogenic variants causing bulldog calf syndrome in cattle. Acta Vet Scand, 62: 49.

Jacinto GP, Häfliger IM, Letko A, Weber J, Freick M, Gentile A, Drögemüller C, Agerholm JS. 2024a. Multiple independent de novo mutations are associated with the development of schistosoma reflexum, a lethal syndrome in cattle. Vet J, 304: 106069.

Jacinto JGP, Letko A, Häfliger IM, Drögemüller C, Agerholm JS. 2024b. Congenital syndromic Chiari-like malformation (CSCM) in Holstein cattle: towards unravelling of possible genetic causes. Acta Vet Scand, 66: 29.

Lerner IM. 1944. Lethal and sublethal characters in farm animals. J Hered, 35: 219-224.

OMIA - Online Mendelian Inheritance in Animals. URL: https://www.omia.org/home/. (accessed date: July 26, 2024).

Seligmann CG. 1904. Cretinism in calves. J Pathol, 9: 311-322.