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Heritable bovine fetal abnormalities

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Abstract

The etiologies for congenital bovine fetal anomalies can be divided into heritable, toxic, nutritional, and infectious categories. Although uncommon in most herds, inherited congenital anomalies are probably present in all breeds of cattle and propagated as a result of specific trait selection that inadvertently results in propagation of the defect. In some herds, the occurrence of inherited anomalies has become frequent, and economically important. Anomalous traits can affect animals in a range of ways, some being lethal or requiring euthanasia on humane grounds, others altering structure, function, or performance of affected animals. Veterinary practitioners should be aware of the potential for inherited defects, and be prepared to investigate and report animals exhibiting abnormal characteristics. This review will discuss the morphologic characteristics, mode of inheritance, breeding lines affected, and the availability of genetic testing for selected heritable bovine fetal abnormalities.

Keywords: Inherited; Congenital; Defects; Cattle; Bovine

1. Introduction

Genetic defects in cattle are being recognized at an increasing rate. As intensive selection concentrates the genetics of select individuals, the potential for emergence or recognition of heritable anomalies may increase. Furthermore, inadvertent propagation of genetic defects in cattle can have detrimental economic impacts and reduce the rate of genetic improvement. Single-trait selection, whether for production or show-ring appeal, has inadvertently increased the frequency of genetic disorders, and surveillance of such disorders has become an important part of bovine health programs. Improved cryopreservation procedures for semen and embryos have accompanied the growth of the AI and ET industries, and in some instances, dissemination of genetic defects has attained international significance.

Recognition and characterization of heritable anomalies has historically relied on an unstructured voluntary system of passive observation, reporting, and investigation. This passive observation system has identified many of the currently recognized inherited disorders. Some countries (i.e., Denmark [1] and France [2]), have recently implemented more intensive surveillance programs designed to increase early recognition of inherited anomalies and to decrease the interval between the index case of a genetic defect and elucidation of its morphologic characteristics and mode of inheritance.

In any detection system, an association between clinical signs and a genetic etiology is more likely to be recognized if an abnormality is clearly evident in

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fetuses or calves, rather than if the onset of signs is delayed. Conversely, genetic defects causing embryonic or fetal mortality, while thought to be prevalent [3,4], may be difficult to recognize and document. A passive surveillance system will be inherently poor at identifying low-prevalence disorders, and may also be compromised by the age at which the defect is first recognizable.

When a potentially heritable fetal abnormality is discounted as a randomly occurring accident of gestation, the defect may not be deemed reportable, and appropriate samples may not be collected. Failure of identification or delay in detection of inherited congenital anomalies may allow further distribution of the mutated genetics.

Any surveillance system, either voluntary or intensive, will be compromised if breeders or veterinarians are unable to recognize fetal anomalies. Obvious defects such as skeletal malformations, extensive soft tissue abnormalities, severe neurological disorders, and diseases of the skin are more likely to be recognized, whereas defects involving internal organs may be less obvious and more easily missed. Surveillance may be further compromised by the reluctance of some breeders to report potentially heritable disorders, or the reluctance of breed associations to aggressively pursue potentially heritable disorders.

For any surveillance programs to be successful, recognition of a potentially heritable defect is but the first step. The anomaly must then be reported, appropriate samples collected and preserved, and pedigree information made available. Although the investigation of heritable bovine fetal anomalies has often been left to those in academia, specifically animal scientists and veterinary pathologists, without the assistance of private practitioners and astute producers, many of the currently recognized inherited disorders of cattle would have gone undiscovered. Veterinarians in the field can play a pivotal role in discovery and surveillance by recognizing and reporting inherited defects of cattle. Reporting of suspected genetic defects in registered stock is generally required, as most breed associations have a genetic defect policy and many also have collaborative relationships with academia. Several comprehensive international reviews on inherited disorders in cattle have been published [5–7] and a regularly updated electronic database, Online Mendelian Inheritance in Animals (OMIA), is available on the worldwide web (http://omia.angis.org.au/) [8].

The purpose of this review is to discuss the morphologic characteristics, mode of inheritance, breeding lines affected, and the availability of genetic testing for selected heritable bovine fetal abnormalities.

2. Brachyspina syndrome

Brachyspina syndrome is a recently reported lethal malformation in the Holstein breed. It was first reported in a Danish Holstein calf in 2006 [9] and has since been reported in five other cases (three in Denmark [10], two in Italy [11]). The syndrome is characterized by calves born dead following a slightly prolonged gestation. The gross morphology of brachyspina syndrome shares many features with short spinal lethal syndrome (SSLS) in cattle, first described in Old Norwegian Mountain calves born in 1930 [12], and later in an Aberdeen-Angus [13] and German Holsteins [14]. There has been morphological variation in all SSLS cases reported; more than one genetic mutation may account for SSLS. Agerholm et al. [9] suggested that SSLS be reserved for cases with close similarity to the Old Norwegian Mountain calves described originally, and that the term brachyspina syndrome be used to describe variant cases sharing some features with SSLS. Brachyspina calves are growth retarded, with severe shortening of the entire vertebral column and limbs (which appear relatively long and slender; Fig. 1). Most vertebral segments have some lack of organization, with irregular ossification separated by cores of cartilage, which prevent identification of individual vertebra (Fig. 2). Multiple defects of the internal organs, including renal dysplasia and intestinal atresia, are consistently present, whereas brachygnatism and caudal dislocation and compression

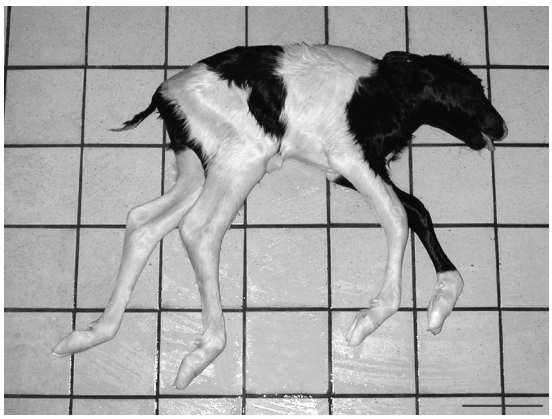

Fig. 1. Bovine brachyspina syndrome in a Danish Holstein calf. The calf has growth retardation with substantial shortening of the spine. Brachygnatism is present and the legs are relatively long and slender. Bar = 15 cm. The photograph is courtesy of Dr. Jørgen Agerholm and reprinted from [10] with permission.

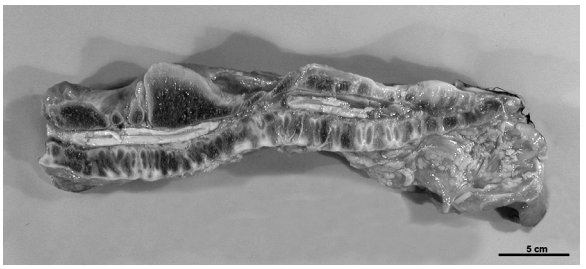

Fig. 2. Widespread malformation of vertebra in a case of brachyspina syndrome. Malformation and disorganization is widespread with cervical, thoracic and lumbar vertebra affected. The thoraco-lumbar junction was not cut on the midline, due to the presence of scoliosis. Bar = 5 cm. The photograph is courtesy of Dr. Jørgen Agerholm and reprinted from [10] with permission.

of the brain are inconsistently present. The appendicular skeleton may or may not be affected.

Although variation in morphology caused by a common syndrome is not unusual, the six reported cases of brachyspina syndrome may have had more than one etiology, since they were not morphologically identical. There was phenotypic variation in other malformations due to single genes, such as complex vertebral malformation (CVM) [15,16] and syndactylism [17]. In two reports of brachyspina syndrome, genealogical examination showed that the cases occurred in familial patterns [10,11], a common ancestor to all parents was found, and the occurrence of the abnormal calves could potentially be explained by transmission of recessive alleles. Although these observations supported the hypothesis of a genetic basis of brachyspina syndrome, association does not prove causation. Widely used sires may occur as common ancestors in the pedigree of malformed calves without that individual being a carrier, or without the defect having an inherited etiology. If brachyspina syndrome is inherited as an autosomal recessive anomaly, it may be an emerging worldwide disease in the Holstein breed.

Currently, a presumptive diagnosis of brachyspina syndrome should be based on the general appearance of abnormal calves. All suspected cases should be reported. A detailed necropsy should be performed, so that variations of the syndrome can be determined and tissues should be collected and DNA samples stored (to aid in establishing an exact diagnosis if a genotyping test becomes available). Breeding trials are needed to determine the inheritance pattern, and breeding data evaluated to determine if increased pregnancy wastage is associated with this syndrome. Questions may be directed to Dr. Jørgen S. Agerholm at the University of Copenhagen (Table 1).

3. Complex vertebral malformation

Complex vertebral malformation syndrome is a recessively inherited lethal disorder which increases

Table 1
Contact information for heritable bovine fetal abnormalities

Anomaly	Contact individual	Laboratories available for testing or breed associations
Brachyspina syndrome	Dr. Jorgen S. Agerholm, University of Copenhagen, Denmark, e-mail: jager@life.ku.dk	na
Complex vertebral malformation	Dr. David Steffen, University of Nebraska-Lincoln, USA, e-mail: dsteffen1@unl.edu	http://www.tieraerztliches-institut.uni-goettingen.de/, http://www.lgscr.it/eng/index.htm
Fawn calf syndrome	New Zealand Angus Association, e-mail: nzangus@beefbreeders.co.nz Angus Society of Australia, e-mail: office@angusaustralia.com.au Dr. Laurence Denholm, e-mail: laurie.denholm@dpi.nsw.gov.au	na
Long nose dwarfism	Dr. James Reecy, Iowa State University, USA, e-mail: jreecy@iastate.edu	www.metamorphixinc.com
Pulmonary hypoplasia with anasarca	Dr. Jonathan Beever, AgriGenomics Inc., e-mail: agrigenomics@prairienet.net	AgriGenomics Inc., 2399 N, 1000 East Rd., Mansfield, IL 61854, USA
Syndactyly	Dr. David Steffen, University of Nebraska-Lincoln, USA, e-mail: dsteffen1@unl.edu	http://www.tieraerztliches-institut.uni-goettingen.de/, http://www.lgscr.it/eng/index.htm, http://www.labogena.fr/, http://www.vhlgenetics.com/vhl/index.html
Tibial hemimelia	Dr. Jonathan Beever, AgriGenomics, e-mail: agrigenomics@prairienet.netInc.	AgriGenomics Inc., 2399 N, 1000 East Rd., Mansfield, IL 61854, USA

Table 2
Numbers and frequency of complex vertebral malformation syndrome carriers among Holstein bulls (modified from [68])

Country	No. bulls tested	CV carrier bulls		References
		No.	%	
USA	11,868	2108	17.76	Holstein Association, USA (2006)
Germany	957	126	13.20	[69]
Poland	605	150	24.79	[68]
Sweden	228	53	23.00	[70]
Japan	40	13	32.50	[21]
Denmark	No data	No data	31.00	[15]

embryonic deaths, abortion, and perinatal death. The condition was first described in the Danish population of Holstein cattle [16] and has since been confirmed in the United States [18], the United Kingdom [19], the Netherlands [20], and Japan [21]. Genealogical research identified Carlin-M Ivanhoe Bell (registration number 1667366), an elite Holstein-Friesian bull born in 1974, to be the main ancestor of cattle carrying this mutation [22]. Due to the superior lactation performance of his daughters, Ivanhoe Bell was extensively used for two decades. Carriers of the CVM mutation exist in Holstein cattle populations worldwide and the frequency of CVM carriers among Holstein sires has reached an alarming level (Table 2).

Complex vertebral malformation fetuses have a composite of phenotypic abnormalities, including axial skeletal deformities such hemi- and misshaped vertebra, ankylosis of mainly the cervico-thoracic vertebra, scoliosis (Fig. 3), symmetric arthrogryposis of the lower limbs, craniofacial dysmorphism, and cardiac anomalies (Fig. 4) [16,22,23]. Clinical heterogeneity among affected calves may make it difficult to make a diagnosis of CVM may be difficult; however, a presumptive diagnosis can be made at necropsy (if pedigree information is available). By comparing DNA sequences of unaffected and affected calves, recent research [15], uncovered a point mutation in the form of a transversion (G to T) in the SLC35A3 gene, causing a valine at position 180 to be replaced with phenylalnine. The SLC35A3 gene product is a golgi-resident transporter critical for the formation of glycoproteins and ultimately axial skeleton development. A screening test (DNA) for CVM is now available and has been widely performed on Holstein sires. Pedigree information now includes the designation ‘‘TV’’ for tested animals free from CVM and ‘‘CV’’ for carriers of CVM. Samples may be submitted to multiple laboratories (http://www.tieraerztliches-institut.uni-goettingen.de/, http://www.lgscr.it/eng/index.htm) to determine if an animal is heterozygous for the CVM genetic mutation, or has two ‘‘normal’’ alleles.

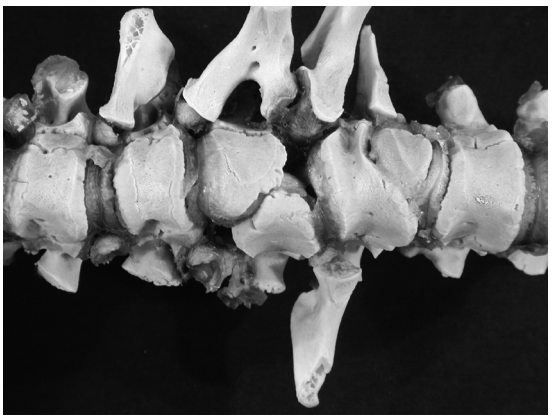

Fig. 3. Malformed thoracic vertebra from a case of complex vertebral malformation in a Danish Holstein calf (Fig. 4). The photograph courtesy of Dr. Jørgen Agerholm and reprinted from [16], with permission from the American Association of Veterinary Laboratory Diagnosticians.

4. Dwarfism

Dwarfism as a heritable condition has been reported in many mammals, including multiple breeds of cattle

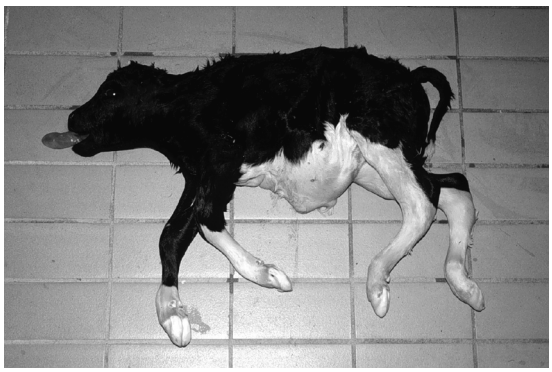

Fig. 4. Complex vertebral malformation in a Danish Holstein calf. Notice the protruded tongue, short neck, and arthrogryposis of the distal joints. The photograph is courtesy of Dr. Jørgen Agerholm and reprinted from [16], with permission from the American Association of Veterinary Laboratory Diagnosticians.

[5,24–30]. Several types of inherited chondrodysplasia have been reported in cattle. Although the phenotypic expression is variable, all are characterized by systemic skeletal disorders, including shortness and deformity of limbs, head and vertebrae. Dwarfism has been recognized in the Angus, Brown Swiss, Danish Red, Dexter, Hereford, Holstein, Japanese Brown Cattle, and Shorthorn breeds [30]. While dwarfism within several of these breeds is the result of genetic mutations in various genes [31–33], no single gene or mutation is responsible for all reported cases of bovine dwarfism. Therefore, a careful physical examination and/or necropsy should be done, and non-genetic causes ruled out. In Northeast Victoria, sporadic outbreaks of chondrodysplasia were linked to congenital manganese deficiency [34]. Persistent infection with bovine viral diarrhea virus may result in stunted or ''miniature'' calves that may be misdiagnosed as dwarfism [35,36].

Dexter Bulldog dwarfism has been a major problem for the Dexter breed since its description in the early 19th century. When defined strictly on the lethal bulldog phenotype, the inheritance pattern of Dexter dwarfism is described as an autosomal recessive trait (i.e., the bulldog dwarf is homozygous for the genetic mutation). However, because heterozygotes have an intermediate dwarf phenotype, the trait can also be described as having an incomplete dominance mode of inheritance. Interestingly, the intermediate dwarf phenotype is the desired short-legged Dexter phenotype, and breeders have been selecting for a phenotype that maintains this lethal allele at high frequency [32]. Homozygosity for the Dexter dwarf mutation is lethal and fetuses are generally aborted at approximately 7-mo of gestation. Clinically, the defective fetuses are characterized by an extreme disproportionate dwarfism, a short vertebral column, marked micromelia, large abdominal hernia, relatively large head with a retruded muzzle, cleft palate and protruding tongue [32]. Bulldog dwarfism of Dexter cattle is caused by two discrete mutations in the aggrecan (ACAN) gene and DNA testing is available for the mutation [32]. Interestingly, in 2003, three cases of ''bulldogs'' in Dexter cattle were reported that did not trace to the known bulldog dwarf carrier bulls (Kalinda Angus, Saltaire Guiness, and Meadowpark Charles). Careful necropsy and investigation revealed that these three cases actually represented Pulmonary Hypoplasia with Anasarca (PHA) in these Dexter cattle [37]. It is noteworthy that cooperation among breeders, veterinarians, and scientists identified the defective gene responsible for the long-standing problem of dwarfism, but also averted potential propagation of the recessive PHA defect in the Dexter breed.

In December 1900, a 2-y-old Hereford bull, St Louis Lad, was transported from the Midwest to the Northeast United States. At the time, no one could imagine the enormous impact St Louis Lad and his 222 registered offspring would have on the Hereford breed in the USA, Canada, Mexico, and Australia. Decades later, as Hereford ''snorter dwarf'' calves were increasingly reported to the American Hereford Association (AHA), it became apparent that the recessive gene responsible for a hereditary form of dwarfism was carried by St Louis Lad, and was well ensconced in the breed. This form of dwarfism in the Hereford breed is an autosomal recessive defect. Homozygotes are described as short and blocky, with deformed growth of the nasal passages resulting in a ''pushed in'' appearance and the typical and audible ''snorting'' when breathing [25,38]. Although experts in cattle judging and in the Hereford breed sometimes claimed to recognize the phenotype of the carriers, they were correct only 50% of the time [39]. This suggests that the phenotype of heterozygotes of the Hereford dwarfs was not consistent and therefore not involved in the extensive propagation of the defect. Conflicting evidence was presented by Marlowe [40], who described phenotypic differences in both Hereford and Angus cattle, based on presumed carrier or clean status. Differences included smaller stature and lesser weight in the presumed carriers, suggesting that selection for phenotype may have played a role in dissemination of the mutation.

A 1956 survey of Hereford breeders in the USA identified 50,000 dwarf-producing animals in 47 states. Through diligent pedigree analysis and breeding trials, the AHA, in concert with breeders and scientists, virtually eliminated the problem from the breed. Because defect-free status was difficult to prove, some entire breeding lines were eliminated. It is remarkable that these breeders were able to muster the collective will necessary to control a recessive genetic defect before the availability of DNA testing, computerized pedigree analysis, and the immediate electronic communication of the modern era. A detailed history of this form of dwarfism and the efforts to eliminate it from the breed is described in ''The Battle of the Bull Runts'' [39], and notes the concurrent existence of dwarf cattle in the Angus breed and in some Angus-Hereford crosses.

Dwarfism in Aberdeen-Angus calves was described in 1951, and determined to be autosomal recessive [26]. The American Angus Association (AAA) handled the issue similarly to the AHA by virtual annihilation of all animals associated with the primary source herd [41]. Following the efforts of the breed association to

eliminate dwarfism, there were no certified reports to the AAA of dwarfism in registered Angus cattle from the 1970s until 2002, although there were anecdotal accounts of unreported cases.

At the start of the 21st century, abnormal Angus calves were reported in several herds in the western U.S. Unlike the previous form of dwarfism, these calves appeared normal at birth, but failed to grow, and after several months appeared to have abnormally short legs and thick bodies. Astute breeders were concerned that these calves were dwarfs. All of the affected calves had multiple pedigree relationships with one Angus cow used extensively in an ET program. Four abnormal calves were sent to veterinary diagnostic laboratories for necropsy; two to the University of Nebraska and two to the University of Washington. Gross and histopathological examination of these calves indicated evidence for diminished endochondral ossification and other features consistent with dwarfism, including the protrusion of the alar wing of the basisphenoid bone into the cranial cavity, abnormalities of the ventral vertebral bodies, and curving of the transverse vertebral processes. Both universities diagnosed these calves as the ''long-nosed'' dwarf.

In the spring of 2002, the existence of six ''long-nosed'' dwarf calves was reported to the AAA. Dr. James Reecy, a geneticist at Iowa State University, obtained DNA from all ancestors in the three-generations preceding the dwarf calves; this served as the starting point to identify the defective gene. In the fall of 2003, a dwarf heifer and her dam (Fig. 5) were donated to Iowa State University. Both the carrier cow and the dwarf heifer were inseminated with semen from a bull known as a dwarf producer, High Valley 7D7 of 4G9 (AAA # 12,838,783; born 1997) and ET was performed to produce additional dwarf calves. Using this genetic material, Dr. Reecy was able to determine that the genetic defect of the long-nosed Angus dwarf was not the same defect as the limbin (EVC2 or LBN) mutation in Japanese brown cattle, nor the ACAN mutation in the Dexter breed [31–33]. Further investigation revealed that the causal mutation of long-nosed dwarfism in American Angus cattle was within exon 15 of the cyclic GMP dependant, type-II, protein kinase (PRKG2) gene. Normal function of the PRKG2 gene is required to allow chondrocyte maturation (J. Reecy, personal communication; [42]). The mutation is 100% concordant with the dwarf, carrier, and wild-type phenotype (J. Reecy, personal communication). Phenotypically, when compared to normal age mates, the long-nosed dwarf fails to grow. The limbs are shortened, but the body is of normal size. There is decreased long bone and vertebral length. Endochondral ossification is incorrect and there is premature calcification of chondrocytes, and osteocytes have a disorganized arrangement and abnormal phenotype.

Fig. 5. On the right is a 3-y-old Angus long-nosed dwarf cow, with her dam to the left. The photograph is courtesy of Dr. James Reecy.

Dr. Reecy's lab group developed a DNA test for detection of heterozygous carriers of the long-nosed dwarf mutation (http://www.freshpatents.com/Genetic-test-for-the-identification-of-dwarfism-in-cattle-dt20071011ptan20070238110.php). Their research was funded, in part, by the AAA and as a consequence, the test has been licensed by AAA to MetaMorphix, Inc. (MMI) Genomics (www.metamorphixinc.com), a commercial laboratory responsible for parental verification for the AAA. According to the AAA, the dwarfism test will be handled like parental verification. Breeders will request a card, the sample will be submitted to MMI, and the results reported to the AAA. It is anticipated that the test will be available in the spring of 2008 (Bryce Schumann, AAA, personal communication). Breeders will be able to utilize the test to assess their herd's genetics through their association with the AAA. This could be advantageous for registered Angus cattle, as samples will be both parentally verified and tested for the mutation, but could be problematic for commercial breeders or breeders registering composite cattle in other herdbooks which use Angus genetics. The gene frequency in the larger registered Angus population will ultimately be determined as the new DNA assay is more broadly applied. Currently, the AAA lists eight males and eight females as carriers of the dwarfism gene (www.angus.org/pubs/defects.html). Five carrier males and three carrier females were born before 1977. Of the recently recorded Angus long-nosed dwarf carriers, all five females and 2 of 3 males were the result of ET, suggesting that not only the use of popular bulls, but also extensive use of ET, can be important in propagation of recessive defects in a population.

Circumstantial evidence from quantitative genetic tools available in the 1950s and pedigree analysis of

family lines most involved with ''snorter'' and the ''long-nosed'' dwarfism, suggests the possibility that both the ''snorter'' and the ''long-nosed'' dwarf may have originated from a single Angus bull imported from Scotland to the USA early in the twentieth century ([43,44]; B. Switzer, personal communication).

5. Fawn calf syndrome

Fawn Calf Syndrome (FCS) is a recently described heritable defect of Angus cattle first reported from Australia, with suspected cases in the USA and several other countries (I. Tammen, http://www.animalgenome.org/community/mail/archive/2665.pdf; L.J. Denholm, personal communication). The syndrome was designated ''Fawn Calf Syndrome'' due to the unusual fawn-like hind limb conformation of affected calves at birth. Mr. Carel Teseling of the Angus Society of Australia (ASA) was one of the first to recognize the heritable nature of the disorder. Since 2001, veterinarians and other scientists from the New South Wales (NSW) Department of Primary Industries, the ASA, the University of Sydney and the University of New England have been investigating cases of this syndrome. These investigations have included parental verification, pedigree analyses, physical examination, necropsy, and quantitative analysis of computer tomography scans of affected calves and their normal siblings. A controlled breeding trial using AI and ET has been conducted. All Australian cases of FCS identified to date have traced to Angus bulls (from the USA) whose semen was imported into Australia.

The key clinical feature of FCS is congenital muscle contracture, resulting in restricted movement of proximal leg joints, particularly in the hind limbs (Fig. 6). Passive movement of the limbs is restricted, which in severe cases is most obvious in the proximal hind limb joints (I. Tammen, http://www.animalgenome.org/community/mail/archive/2665.pdf; L.J. Denholm, personal communication). Abnormal muscle contracture decreases dramatically as a calf ages, although muscle development always remains poor (L.J. Denholm, personal communication). Australian researchers describe FCS adults as ''tall and skinny''. The FCS pattern of congenital proximal joint contracture with distal joint hyperlaxity is most pronounced in the hind limbs and readily distinguished from the congenital distal joint flexion contracture observed sporadically in the forelimbs of large calves that experience movement restriction due to ''crowding'' *in utero* (L.J. Denholm, personal communication).

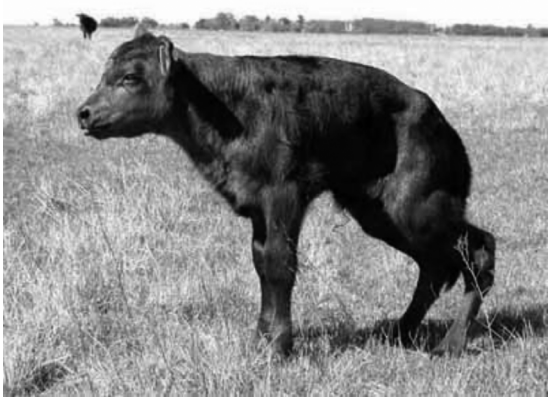

Fig. 6. Fawn calf syndrome in an Angus calf. Note the long and straight hind limb conformation and the poor muscle development. The photograph is courtesy of the Australian FCS research group.

Affected calves appear taller than expected and there is increased angulation in the stifle and hock joints, in addition to kyphosis. Severely affected calves may have pronounced scoliosis leading to bilaterally asymmetric hind limb conformation. Severely affected FCS calves are culled or die at an early age, due to their inability to stand to nurse or walk. Less severe cases may survive to maturity, with apparently normal fertility. Based on breeding trials, the Australian researchers concluded that FCS was a heritable genetic disorder, probably with a simple recessive mode of inheritance (C. Teseling, Angus Society of Australia, see pedigree diagrams at http://s84.photobucket.com/albums/k34/CarelT/).

Although necropsy may provide additional information, a diagnosis of FCS is usually possible following careful clinical examination. The hallmarks of FCS are: congenital proximal limb contracture; congenital kyphosis (or scoliosis in severe cases); congenital distal limb hyperlaxity; marfanoid conformation [arachnodactyly (spider fingers/abnormally long and slender digits) and dolichostenomelia (tall and slender with long appendages)]; muscle hypoplasia; a profound reduction of the clinical severity with growth and maturity; and consistent pedigree tracing to an identified suspect founder animal on both sides of the pedigree (L.J. Denholm, personal communication).

All FCS affected calves born in Australia for which pedigree data are available trace to one or more of four bulls from the USA whose semen was imported into Australia. All of the four USA Angus ''FCS carrier'' bulls identified in Australia are descended from the same USA Angus ''suspect founder'' cow. In the USA, all of the suspected fawn calves whose pedigrees have been examined by Dr. William Switzer, with one exception, trace to these same bulls and the suspect

founder cow. Interestingly, the calf that is the exception traces twice to an ancestor of the suspect founder cow (WP Switzer, personal communication). Cases of FCS in Angus calves have also been reported to the Australian researchers from other countries, where semen from the same bulls from the USA has been used.

In recent years, the majority of ''fawn calves'' born in Australia have been sired by one particular AI bull from the USA, a direct-line descendent of the suspect founder cow identified by pedigree analysis in Australia. This bull has one of the two original progenitor bulls in the maternal ancestry, and is also the sire of fawn calves produced in the controlled experimental breeding of direct line progeny of the two original bulls in Australia (C. Teseling, Angus Society of Australia, see pedigree diagrams at http://s84.photobucket.com/albums/k34/CarelT/). Four of 14 of the calves produced in this experimental breeding trial were affected (L.J. Denholm, personal communication; http://www.advantagecattle.com/forum/topic.asp?TOPIC_ID=1959&whichpage=3).

The current prevalence of FCS in the Angus population in the USA is unknown. Several bulls that have sired affected calves in Australia had substantial dissemination of their genetics by AI within the USA, and at least one bull that has sired FCS calves in Australia remains an influential sire of sons in the USA. Experience with CVM in the worldwide Holstein population is a clear illustration of the impact that a popular sire can have within an international breed population, and underscores the importance of international surveillance and reporting of suspected genetic diseases of livestock. The considerable use of Angus genetics to produce composite animals registered in herd books of other breeds makes FCS a potential concern beyond the registered Angus population.

Characterization of the full spectrum of abnormalities in the disease is ongoing and more cases are needed to refine the diagnostic criteria. Affected calves should be identified and parentally verified. In the USA, calves potentially affected with FCS should be reported to Bryce Schumann at the AAA and the AI company/distributor. Dr. David Steffen (University of Nebraska) is interested in obtaining cases to further characterize the pathology and Dr. Jim Reecy at Iowa State is interested in identifying the defective gene. Australian investigators are seeking additional cases for their research; contact persons are Carel Teseling at the ASA or Dr. Laurence Denholm of the NSW Department of Primary Industries. The New Zealand Angus Association is also soliciting case reports. To contact Angus breeders in Australia and North America these investigators have published a pamphlet (I. Tammen, University of Sydney; http://www.animalgenome.org/community/mail/archive/2665.pdf) and provided detailed information on the web: (http://www.advantagecattle.com/forum/topic.asp?TOPIC_ID=1959&whichpage=1)

6. Inherited Congenital Myoclonus

Originally known as hereditary neuraxial edema, Inherited Congenital Myoclonus (ICM) is an autosomal recessive disease of Polled Hereford and Polled Hereford cross calves, first reported in 1969 [45]. Calves can be affected with spontaneous myoclonus (brief, involuntary twitching of a muscle or a group of muscles) *in utero*, resulting in distinctive fractures in the acetabulum or head of the femur. Affected calves are often born 1 week premature and characterized by hyperesthesia and myoclonus, which may occur spontaneously or in response to tactile, visual, and auditory stimuli. One of the first signs is a myolonic response to the dam licking the calf. Affected calves are bright and alert, but unable to stand. Euthanasia is recommended. If left unattended, calves usually die shortly after birth.

There are no recognizable lesions in the central nervous system and antiepileptic and anticonvulsive drugs do not control symptoms [46]. Bovine ICM has been attributed to a severe disturbance of glycine-mediated neurotransmission in the spinal cord [46,47]. Spinal cord sections and membrane preparations from affected animals had a specific and marked deficit in [^{3}H]strychnine-binding sites. A molecular lesion in the α1 subunit of the glycine receptor underlies the phenotype observed in bovine ICM. A nonsense mutation in codon 24 results in a truncation of the α1 subunit of the glycine receptor polypeptide and subsequent loss of cell-surface expression [48]. In Australia, ICM genotyping of DNA from tail hair roots of sale-yard bulls estimated the prevalence of carriers (heterozygotes) for ICM to be from 1.0 to 2.0% [49]. Unfortunately, at present, the DNA test for ICM is not commercially available (PR Schofield Executive Director and CEO of Prince of Wales Medical Research Institute, personal communication).

7. Perosomus elumbis

Perosomus elumbis (PE) is used to describe a phenotypic set of congenital defects that includes agenesis of the lumbosacrocaudal spinal cord and vertebra, arthrogryposis or ankylosis of hypoplastic hind limbs (Fig. 7), and soft tissue malformations of

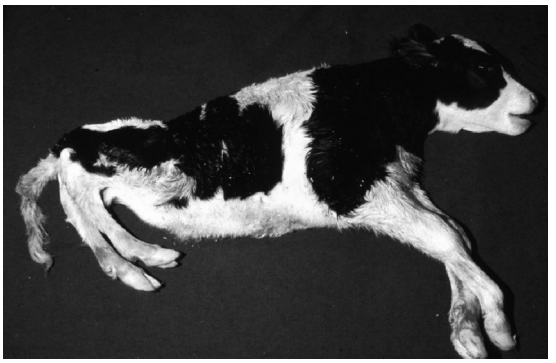

Fig. 7. Full-term Holstein fetus with perosomus elumbis. Note the normal forelimbs and the hind limb arthrogryposis. The photograph is courtesy of Dr. Dean Percy (Professor Emeritus, Ontario Veterinary College) and reprinted with permission from Dr. Percy and Noah's Arkive (University of Georgia).

abdominal viscera, urogenital, and anorectal systems. Perosomus elumbis is reported most frequently in cattle [50,51], but has also been described in small ruminants [52,53], pigs [54], and in humans as a mild equivalent (caudal regression syndrome) [54,55]. Characteristically, affected calves are born dead at term or die perinatally. Dystocia is a frequent consequence of the hind limb abnormalities, and delivery may require partial fetotomy or Cesarean section. Although the etiology of this malformation is unknown, it was believed by Dr. H. Leipold to be hereditary, at least in the Holstein breed, where he encountered 25 cases from 1986 to 1992 [50]. More recent findings in the areas of developmental biology, clinical and molecular genetics, and epidemiology suggest that PE should be considered as a primary polytopic development field defect caused by abnormalities in the homeobox (*Hox*) gene family. *Hox* are responsible for craniocaudal patterning of derivatives of all three germ layers. Abnormal *Hox* expression caused by gene mutation (inherited sacral agenesis in humans; [56]) or aberrant transcription factors (retinoic acid; [57]) leads to vertebral agenesis in the caudal half of the body and severe visceral malformation similar to PE. Abnormal *Hox* expression or function may be implicated.

8. Pulmonary hypoplasia with anasarca

Pulmonary hypoplasia with anasarca (PHA) is a lethal autosomal recessive disorder characterized most notably by dystocia, profound anasarca, death of the calf, and not uncommonly, death or morbidity of the cow [71,72]. It was noted by Dr. Chuck Hannon, who identified three distinct patterns of deformed calves: one compatible with what we now know is Tibial Hemimelia (TH); the second compatible with what is now designated as PHA; and the third were calves that had both lethal mutations.

Originally PHA calves were identified as Maine-Anjou, Shorthorn or their crosses. The apparent link was three popular bulls: two registered Maine-Anjou bulls (Draft Pick, born 1989; AMAA # 165,744 and Stinger, born 1985; AMAA # 111,205) and a bull registered with the American Chianina Association (Payback, born 1992; ACA # 232,907). Subsequent genetic testing suggested a common ancestor of the three bulls. Because Draft Pick had the most complete pedigree and the largest number of samples available, an informative pedigree was developed and used to identify the defective gene (J Beever personal communication). In that regard, PHA is the result of a single mis-sense mutation common to Draft Pick, Stinger, and Payback, and identified in modern Shorthorn, Maine Anjou, and composite cattle.

Draft Pick's maternal great grand sire, Paramount (AMAA # 77; born 1973), a full-bood Maine-Anjou bull exported from England to Canada, was a PHA carrier. Due to incomplete or inaccurate pedigrees or inability to obtain samples from older full-blood Main-Anjou cattle, the origin of the mutation in Stinger and Payback has not been positively identified. Molecular markers surrounding the gene suggest the French import Dalton (AMAA # 15; born 1970) as a common source for Stinger and Payback.

In the USA, the Maine-Anjou breed is considered the origin of PHA. In registered Maine-Anjou cattle, Draft Pick is primarily responsible for the widespread dispersion of the mutation, whereas in registered Shorthorn cattle, Stinger is considered primarily responsible. Paramount is also found in the pedigrees of some registered Shorthorn cattle. One registered half-blood Simmental bull, the son of a Stinger cow, has been identified as a PHA carrier. In crossbred, composite or ''club calf'' cattle, the origin of the defect cannot always be determined.

Breeding of two PHA carriers would theoretically produce 25% affected fetuses. However, there appears to be a high percentage of pregnancy wastage from approximately 90–200 d of gestation. When PHA fetuses survive to near term, they invariably result in dystocia. It appears that PHA calves thought to be ''bred to the AI date'', are usually premature births of calves conceived due to natural service following an AI program.

The most obvious external characteristic of PHA calves is marked anasarca, resulting in large calves

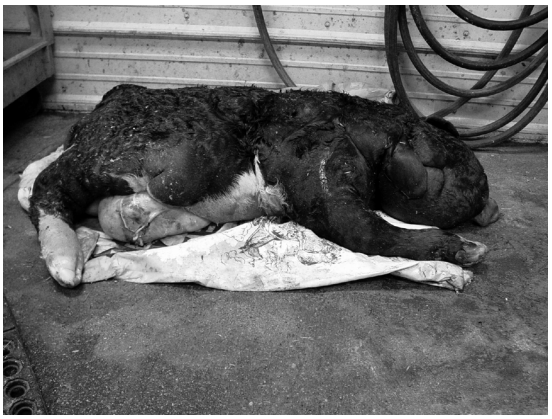

Fig. 8. Calf with PHA delivered by Cesarean-section. The calf was sired by a Maine-Anjou bull out of a composite cow registered with the American Chianina Association. Note the severe anasarca. The photograph is courtesy of Dr. Lana Kaiser.

(Fig. 8), frequently requiring a Cesarean section. There are some reports of PHA fetuses weighing in excess of 90 kg and cows requiring euthanasia because the fetus could not be removed without substantial damage to the cow [71,72]. Furthermore, PHA is characterized by the absence or near absence of lung tissue (pulmonary hypoplasia; Fig. 9), anasarca secondary to lymphatic agenesis (absence of lymph duct and nodes), and athymia [58,71,72].

Heterozygous PHA carriers have a ''normal'' phenotype and can be identified only by genetic testing. Following identification of the gene in late 2006, over 40 popular Maine-Anjou, Shorthorn, and ''club calf'' sires were identified as PHA carriers. Interestingly, several of the most popular Shorthorn bulls are carrier

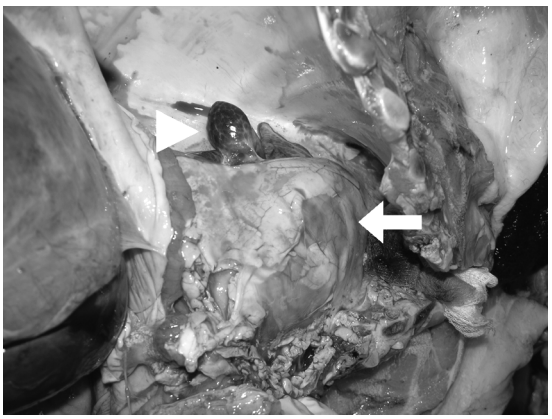

Fig. 9. Right hemi-thorax of a calf with PHA. While the lungs of a ''normal'' bovine fetus at a similar stage of gestation are proportionate to those of a neonate, note the severe pulmonary hypoplasia (arrow = heart covered by pericardium; arrowhead = severely hypoplastic lung). The photograph is courtesy of Dr. Anita Varga.

for both TH and PHA. A syndrome similar to PHA was identified in Dexter cattle in 2006 when Windsor et al reported three cases of PHA in the Dexter breed [37]. The cows were related and the inheritance was felt to be autosomal recessive. Although the mutation in the Dexter breed involves the same gene as the condition seen in Maine cattle, it is not the identical defect. The Maine-Anjou mutation was a simple point mutation, whereas the Dexter mutation was an 84 base pair deletion involving the same exon as the Maine mutation (J, Beever, personal communication).

Practitioners should be aware of the potential occurrence of PHA-like conditions in other breeds. In the fall of 2007, a veterinary student on an externship in the southeastern USA observed a case of dystocia in a Hereford cow that resulted in a Cesarean section. The student recognized similarities between the calf delivered and PHA cases he had seen at Auburn University College of Veterinary Medicine. The Hereford calf was submitted for necropsy at the University of Nebraska, where it was described as having many morphological similarities to the syndrome seen in Maine cattle. This resulted in the first reported case of PHA in a Hereford calf (D. Steffen, personal communication). The dam of the PHA Hereford calf tested negative for both the Maine-Anjou and Dexter mutation (J. Beever, personal communication). Whether this case represents an inherited condition in Hereford cattle similar to PHA is unknown (D. Steffen, personal communication), but it highlights the importance of recognition and investigation of potentially heritable defects. Communication with experts, submission of abnormal calves to qualified diagnostic laboratories, records of pedigree data, and banking of tissues for genetic analysis could prove invaluable, should other similar cases occur.

9. Syndactyly

Syndactyly in cattle is also called ''mulefoot'' and refers to the fusion or non-division of the two functional digits of the bovine foot with synostotic (fusion of normally separate skeletal bones) phalanges (Fig. 10). Phalanges are synostotic horizontally and by pairs; the second pair of phalanges is most fully synostotic, followed by the third, and then the first. This abnormality is often subject to a right-left and a front-rear gradient, being most often seen in the front and right feet. Proximal limb structures can also be affected in syndactylous animals, resulting in a reduced number of sesamoid bones. Synostotic phalanges can be detected as early as 37–40 d post-coitum in the bovine embryo.

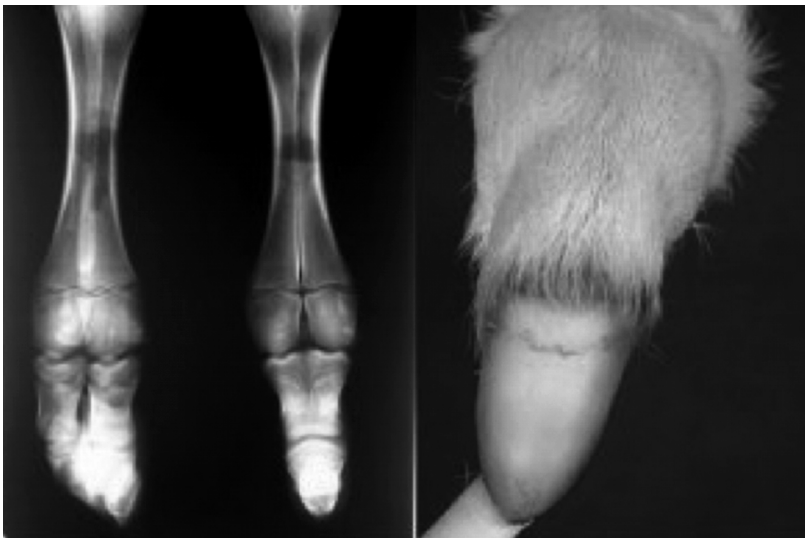

Fig. 10. Holstein calf with affected syndactylous forefeet [60].

Bovine syndactyly is an autosomal monogenic recessive trait with incomplete penetrance (~79% in Holstein cattle) and variable expression. Crossbreeding experiments between Holstein and Aberdeen-Angus have produced syndactylous progeny, suggesting a common locus responsible for the disorder in both breeds. The bovine syndactyly locus was localized to chromosome 15 in 1996 [59] and is due to mutation in the low-density lipoprotein receptor-related protein 4 gene (*LPR4*) [17,60,61]. The occurrence of syndactylous cattle peaked in the 1970s as carrier animals were indirectly selected for superior production of milk and butterfat. The development of test mating and genetic testing greatly reduced the incidence of syndactyly. Unfortunately, syndactylous animals are still occasionally observed in the Holstein population and some carrier animals are still being used for breeding. Eradication of syndactyly will require a precise method to detect the causal genetic mutation. Unfortunately there is extensive allelic heterogeneity in *LPR4*, with the six independent mutations described still not accounting for all analyzed cases [17,60,61]. The two most frequent mutations are the Holstein-specific exon 33 mutation [17] and the Angus-specific exon 37 mutation [61]. Because not all causal mutations have been detected, genetic testing for the carrier status of single individuals remains difficult. Several labs offer testing for the known genetic mutations [Germany (http://www.tieraerztliches-institut.uni-goettingen.de/); Italy (http://www.lgscr.it/eng/index.htm); France (http://www.labogena.fr/); the Netherlands (http://www.vhlgenetics.com/vhl/index.html)]. Unfortunately, each laboratory utilizes different technologies and seldom analyze for the same genetic mutations.

The American Angus Association lists the status of several bulls and cows as carrier or free of the mutations responsible for syndactyly. However, this freedom from carrier status is based solely on progeny test information, and could be questioned in the context of the allelic heterogeneity of syndactyly in Holstein cattle.

10. Tibial hemimelia

The Tibial hemimelia syndrome was first described in 1951 in Scotland in the Galloway breed of cattle [62]. This lethal condition is characterized by multiple congenital skeletal deformities, most notably shortened or absent tibia, abdominal hernia, cryptorchidism, failed Müllerian duct development, hirsutism, and improper neural tube closure, resulting in meningocele (Fig. 11). Calves are born dead or die shortly after birth. The Scottish Galloway Association used test breeding and pregnancy termination to identify carriers and eliminate the autosomal recessive defect from Galloway breeding stock [63].

The syndrome was first described in the USA in 1974 [64], and subsequently in a case report of a female Simmental calf with arthrogryposis, ventral abdominal hernia, tibial hemimelia and the nonunion of Müllerian ducts, with the suggestion that it might be a genetic disorder [65]. A decade later, TH was identified in six genetically related registered Shorthorn calves, three from the USA, and three from Canada [66]. Although the skeletal abnormalities varied, the combination of tibial hemimelia, abdominal hernia and meningocele was felt to be strikingly similar to the condition previously described and determined to be inherited as

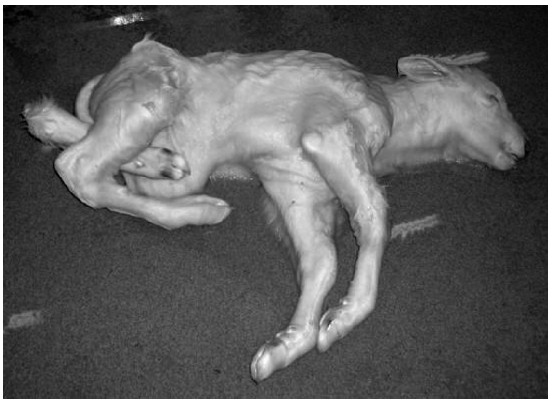

Fig. 11. Tibial hemimelia in a Shorthorn calf. Note the twisted hind limbs and the large abdominal hernia. The calf also had a meningocele and cryptorchidism. The photograph is courtesy of Dr. Chuck Hannon.

an autosomal recessive trait in Galloway cattle. Pedigree analysis of the Shorthorn calves suggested that homozygozity of an autosomal recessive allele was responsible for the defect.

It is interesting that the phenotype of the heterozygote (straight hind limbs and long shaggy hair coat) was considered desirable in the show ring and frequent use of popular sires lead to excessive inbreeding and increased allele frequency due to selective pressure. The occurrence of affected calves was increasingly noted after 2000. Dr. Chuck Hannon and Shorthorn breeders in the mid-west cooperated to provide tissue samples and pedigree information to Dr. Jon Beever and Brandy Marron, ultimately resulting in identification of the defective gene mutation [67,71]. The mutation was traced to the Irish bull Deerpark Improver (ASA # 3,684,142; born 1972), one of a few direct imports to North America. Improver was used extensively in the U.S. in the 1970s, as there are 635 direct progeny registered with the American Shorthorn Association. The defective gene has been shown to be aristaless-like homeobox 4 (ALX4), a major regulator of hind limb formation (J. Beever, personal communication). The Improver deletion removes approximately one-third of the ALX4 gene, including the upstream regulatory sequence and involves approximately 46,000 base pairs**.** After identification of the Improver deletion, it was noted that although the parentage of some TH calves was DNA-verified, some parents did not test positive for the Improver deletion. Additional studies revealed that the bull TKA Outcast (ASA # 4,046,304; born 2001) possessed a larger deletion of 450,000 base pairs that overlapped the Improver deletion, and removed four genes, including ALX4. The Outcast deletion is rare and affected calves sired by Outcast were ''compound heterozygotes'' (heterozygous with the Improver mutation on one chromosome and the Outcast mutation on the other). Although ''heterozygous'', these calves were affected like those homozygous for the Improver deletion. The frequency of the Outcast mutation is so low, and the magnitude of the deletion so much larger, that it is unlikely that there have been any TH calves homozygous for the Outcast deletion. Because samples from the Scottish Galloway cattle are unavailable for testing, it is unclear whether the Improver or Outcast deletions in Shorthorns originated from the Galloway breed or are different mutations.

The popularity of the TH phenotype has led to extensive use of carrier bulls in the club calf and show cattle arena. A substantial number of cattle registered with the Shorthorn, Maine Anjou, Chianina breed Associations, as well as crossbred or composite cattle, are known to carry the defective gene. In 2004, more than half of the top 10 sires for a number of Shorthorn registrations were putative carriers. In 2005, 21 of 24 black composite AI sires offered by a single vendor were verified as carriers.

In a 2007 sire directory of popular ''club calf sires'', one-third of bulls were TH carriers, including clones and sons of a popular TH carrier bull. Of the 10 most popular Shorthorn AI sires for 2006 calves, three were carriers for both TH and PHA and one was a carrier of TH (Shorthorn Country, April 2007).

11. Conclusion

The best control for heritable diseases is to avoid breeding carriers of genetic mutations. Unfortunately, many carriers of heritable defects have a normal and desirable phenotype. This, coupled with the lack of molecular diagnostics available to detect many genetic causes of bovine congenital anomalies, makes prevention a challenge. Commercial beef producers rarely have problems, as they often use crossbreeding systems. Purebred operations, whether beef or dairy, may encounter varying frequencies of defects as a result of consanguineous breeding, particularly for fetal abnormalities resulting from an autosomal recessive inheritance pattern.

When congenital defects appear in a herd or breed, non-genetic causes of the defects should be investigated and ruled out. Pedigree information should be examined and verified. The presence of known carriers of heritable congenital anomalies within the pedigree of an affected calf or fetus is highly suggestive of a genetic etiology. If available, genetic testing of tissues from the dam, sire, affected calf or even the sire's semen, may be

useful when the carrier status of the ancestors is unknown or in question. When no evidence of heritable congenital anomalies exists in the pedigree, the practitioner and herd owner should be cognizant that the abnormality may represent a new or previously unreported defect.

If a new anomalous condition appears, or if a specific diagnostic test is not available, test mating of animals that have produced calves/fetuses with the specific trait or sire-daughter/dam-son matings may be performed to further characterize the inheritance pattern(s); however, this is time consuming and expensive. Additionally, if the recessive trait is lethal, the timing of the conceptus death may alter the outcome of the test matings. Two examples of how timing of conceptus demise as a result of heritable defects might alter the perceived outcome of test matings are embryonic deaths resulting from CVM and single nucleotide polymorphisms (SNP) of the *STAT5A* gene. Embryonic mortality as a result of CVM has been recognized as a delayed return to estrus or an abnormal interestrus interval or even as pregnancy loss following early pregnancy diagnosis, as 16% of CVM-affected embryos die by 56 d after conception, and fetal mortality rates increase to 45 and 77% by 150 and 300 d after insemination, respectively [23]. Conversely, a recent publication suggests that in the case of SNPs within the *STAT5A* gene, decreased fertilization rates and early embryonic death (prior to maternal recognition of pregnancy) resulted in apparently normal interestrus intervals, which may have contributed to delayed identification of this mutation. Failure to recognize that embryonic loss was occurring may have contributed to a higher prevalence of the mutated allele of the *STAT5A* gene associated with embryonic lethality, suggested to be present in approximately 40% of the Holstein population [4].

While AI and ET can propagate undesirable genes, these technologies are also useful for identifying such genes and determining the mode of inheritance. Widespread use of AI constitutes a progeny test of a bull's inheritance (positive and negative attributes). With good surveillance and reporting programs, undesirable genes can be identified more quickly in widely used AI sires than following limited use in natural service. Furthermore, AI and ET are very useful technologies for breeding trials.

As succinctly stated by Sir Francis Bacon, ''Knowledge is power''. At present, knowledge can be freely and instantaneously exchanged; electronic communications allow the exchange of information among breeders, veterinarians and scientists. An ongoing, open dialog among these groups enhances the potential for early description of syndromes or abnormal calves, and should reduce the genetic and economic consequences of heritable congenital mutations in cattle.

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