HERITABLE BIRTH DEFECTS IN CATTLE

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Abstract

Inherited congenital anomalies are probably present in all breeds of cattle and propagated as a result of specific trait selection. In some breeds, the occurrence of inherited anomalies has become frequent, and economically important. Veterinarians, animal scientists, and cattle breeders should be aware of inherited defects, and be prepared to investigate and report animals exhibiting abnormal phenotypes. This review will describe the morphologic characteristics, mode of inheritance, breeding lines affected, and the availability of testing for selected (newly described) heritable bovine fetal abnormalities.

Introduction

Genetic defects in cattle are being recognized at an increasing rate and genetic testing has changed cattle production – not only in terms of traits beneficial to production, but also in the ability to identify and manage harmful genetic defects. As selection concentrates the genetics of certain individuals, the potential for emergence of heritable anomalies increase. The surveillance of such disorders has become an important part of bovine health programs.

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. 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 to report potentially heritable disorders, or the reluctance of breed associations to aggressively pursue potentially heritable disorders.

Several reviews on inherited disorders in cattle have been published (Huston et al., 2000; Leipold et al., 1983; Whitlock et al., 2008) and a regularly updated electronic database, Online Mendelian Inheritance in Animals (OMIA), is available on the worldwide web (http://omia.angis.org.au/) (Nicholas, 1998). The purpose of this review is to discuss those heritable bovine fetal abnormalities recently described for which the mutation has been identified and a test is available.

Arthrogryposis Multiplex

Arthrogryposis Multiplex (AM; "Curly Calf Syndrome") is a lethal autosomal recessive genetic defect that originated in Angus cattle. Beginning in 2008, researchers in collaboration with the American Angus Association (AAA) investigated abnormal calves believed to fit the description of what was then called AM and commonly referred to as "Curly Calf Syndrome" in Angus cattle. Within 2 months, researchers obtained samples and pedigrees from affected calves and their parents, the mutation was identified, the DNA test was developed and validated, and the status of over 700 AI bulls was determined (American Angus Association, 2010a).

The genetic cause of AM was suspected when pedigree analysis of the original cases found that all affected calves trace on one or both sides of their pedigree to GAR Precision 1680. Later investigation revealed that those AM calves that did not trace to 1680 on both sides of the pedigree did trace to his dam 9J9 GAR 856 whose sire Rito 9J9 of B1567T26 has subsequently been determined to be a carrier of AM (Kaiser, 2009).

Calves with AM are born dead or die shortly after birth. They are small for gestational age and have markedly diminished muscle mass. It appears that in AM an essential protein that allows communication between nerves and muscle tissue is absent, thus the calf (which fails to move *in utero*) is born with the joints of all 4 limbs fixed and the legs twisted. There are several characteristics of AM including arthrogryposis (fixed, twisted joints), kyphoscoliosis (twisted spine), and decreased muscling (American Angus Association, 2010a) (Figure 1).

The mutation is a deletion that involves 3 genes – one of these genes is involved in the development of nerve and muscle. Affected calves are missing ~23,000 base pairs. These missing base pairs results in complete loss-of-function of all three genes in homozygous calves (Kaiser, 2009). A genetic test is available through several laboratories [AgriGenomics, Igenity, Pfizer, GeneSeek, and MetaMorphix, Inc. (MMI)] to determine if an animal carries the AM mutation.

Neuropathic Hydrocephalus

Neuropathic Hydrocephalus (NH) is a lethal autosomal recessive genetic defect of Angus cattle. At the same time that AM calves were being submitted, calves with hydrocephalus were also submitted. These calves were similar in description and pedigree to calves described by Dr. Denholm in Australia. Interestingly, calves submitted for both AM and NH generally had GAR Precision 1680 on both sides of the pedigree.

Affected NH calves are born near term and weigh 25-35 pounds at birth. The head is markedly enlarged (Figure 2A). The bones of the skull are malformed and appear as loosely organized bony plates that fall apart when the head is opened (Figure 2B). The cranium is filled with fluid and no recognizable brain tissue is evident. The spinal canal is also dilated and no observable spinal tissue is found (American Angus Association, 2010c).

Neuropathic hydrocephalus is the consequence of single DNA base pair mutation on both alleles. The genetic mutation results in the abnormal function of an important protein that is involved in

the development and maintenance of the central nervous system resulting in the NH syndrome (American Angus Association, 2010c). The NH mutation likely originated with the bull GAR Precision 1680 as both his sire and dam test negative for NH (American Angus Association, 2010c).

Nearly 10% of AI sires representing a broad cross section of registered Angus genetics were found to be carriers of NH (Beever, 2009). Given the number of calves reported this frequency appeared to be higher than expected. This phenomenon could be explained by a relatively high percentage (50% to 70%) of pregnancy wastage in NH embryos and/or fetuses. This is consistent with what is known about mutations in this gene for other species (i.e. complete disruption of this gene in mice results in 100% fetal mortality before the halfway point of gestation) (Beever, 2009). Genetic testing to determine if an animal carries the NH mutation is available through many of the same laboratories providing testing for AM (AgriGenomics, Igenity, Pfizer, and MMI).

Congenital Contractural Arachnodactyly

Congenital Contractural Arachnodactyly (CA), also known as "Fawn Calf Syndrome", is a non-lethal autosomal recessive genetic defect of Angus cattle. CA calves are normally born alive and most can walk, suckle, and survive. The birth weight of FCS calves is "normal". The phenotype is subtle and hence CA may not initially be recognized as a defect. CA is a developmental defect involving reduced elasticity of the connective tissue of muscles, first identified in Victoria, Australia in 1998 but now reported in many countries (Denholm, 2010). Although CA is a less severe disease than lethal genetic defects of Angus calves, without human intervention up to 20% of CA calves die soon after birth, simply because they are unable to stand and suckle (Denholm, 2010). To make the diagnosis in a newborn calf, it is necessary that all the following are observed:
Congenital proximal limb contracture;
Congenital distal limb hyperextension;
Congenital kyphosis; and
Significant post-natal improvement in these clinical signs as the calf grows and matures (Denholm, 2010).

Since 2001, veterinarians and other scientists have been investigating CA in Angus cattle from Australia, with suspected cases in the USA and several other countries (Whitlock et al., 2008). These investigations have included parental verification, pedigree analyses, physical examination, necropsy, and quantitative analysis of computer tomography scans of affected calves and their unaffected siblings. In 2004 Australian researchers demonstrated the genetic control of CA by embryo transfer matings of putative carrier sires to affected females. Those matings produced claves affected with the CA pathology in a proportion consistent with recessive inheritance. All Australian cases of CA identified to date have traced to Angus bulls (from the USA) whose semen was imported into Australia.

Researchers have identified the genetic defect that causes CA and have partially characterized the specific mutation responsible for CA as a deletion of at least 38,000 DNA base pairs that removes a significant portion of this gene severely compromising its function (American Angus

American Angus Association, 2010b). The complete sequence of the deleted DNA segment is not known making it currently impossible to develop a diagnostic test that is 100% accurate (American Angus Association, 2010b). Until recently the breed associations (AAA and Angus Australia) have avoided identifying any animal as a CA carrier because the current diagnostic test is less than 100% accurate (Steffen and Beever, 2009). However, some specifically identified animals have been named as either carriers or are "highly likely" to be carriers of the CA mutation by Angus Australia (American Angus Association, 2010b). The current assay generates some false positives in a number of pedigrees creating a significant danger of misinterpretation of test results. The current test does allow an overall estimation of frequency of the CA mutation in the population. With more than 500 animals genotyped with several of the genetic markers for CA the maximum frequency of CA in the AI sire population is approximately 3 to 4% (American Angus Association, 2010b).

Idiopathic Epilepsy

Idiopathic Epilepsy (IE) is a seizure disorder caused by an autosomal recessive genetic defect and is incompatible with life. IE is predominately seen in horned Herefords, but can be seen in polled Herefords with horned animals in their pedigrees. Affected calves can have their first seizure anywhere from birth to several months of age and they have a "normal" phenotype when they are not seizing. Environmental stressors (heat, cold, weaning, etc…) can trigger the seizures and the seizures can last from minutes to more than an hour.

There had been reports about a seizure disorder in Herefords for some time. Scientist began receiving reports of seizing calves and samples from them in 2003. Subsequently, tissue from *in vivo* fertilization using suspected carrier cows and bulls was used to identify the mutation (Kaiser, 2009). Over 15,000 Hereford samples have been tested for IE. To date all carriers of IE trace to a single bull born in 1982, however DNA is not available to test this bull.

The mutation is more complicated than a single substitution or deletion. DNA base pairs are duplicated and deleted, with the result being an addition of 5 base pairs (Kaiser, 2009). A DNA test is available through several laboratories (AgriGenomics, American Hereford Association, and Igenity) to determine if an animal carries the IE mutation.

Osteopetrosis

Osteopetrosis (OS; Marble Bone) is a lethal autosomal recessive genetic defect previously identified in humans and a long list of animals. Cattle breeds known to be affected are Black and Red Angus, Hereford, Simmental, and Holstein. The defect was most recently reported in Red Angus cattle (Nietfeld, 2007). Calves affected with OS are born 10 to 30 days early. They usually have head abnormalities that consist of brachygnathia inferior, impacted molars, and a protruding tongue. The long bones are shorter than normal, the marrow cavities are filled with unreabsorbed bone (primary spongiosa), but are very fragile and can be easily broken (Nietfeld, 2007).

Samples from identified carriers were used to identify the mutation. The disease is caused by a deletion of a gene necessary for bone remodeling during development (SLC4A2) (Kaiser, 2009).

Genetic mutations that cause OS in Red Angus and Black Angus cattle are not the same. However, the mutation in Black Angus has not been identified. This could mean that the mutation in Black Angus changed or that they are 2 distinctly different mutations. Genetic testing is available through AgriGenomics, Pfizer, MMI Genomics, and Igenity. However, the OS test is for the mutation in Red Angus only.

Conclusion

In recent years, there have been several defects identified that have had significant impact on specific cattle populations. The cooperation of molecular geneticist, veterinary pathologists, breeders, and breed associations have identified genetic disorders, characterized the pathology, determined the genetic mutations and then developed tests. In the very near future, it is likely that the genetic mutations in other heritable congenital defects of cattle will be identified through similar collaborative efforts.

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 producers, many of the currently recognized inherited disorders of cattle would have gone undiscovered. For any surveillance programs to be successful, recognition of a potentially heritable defect is but the first step. The anomaly must be reported, appropriate samples collected and preserved, and pedigree information made available. Veterinarians in the field can play a pivotal role in discovery and surveillance by recognizing and reporting inherited defects of cattle.

Figure 1. Arthrogryposis Multiplex in a Angus calf that was born dead. Notice the contracted forelimbs and extended hindlimbs. This photograph is courtesy of Dr. Robert L. Carson of Auburn University, AL.

A

B

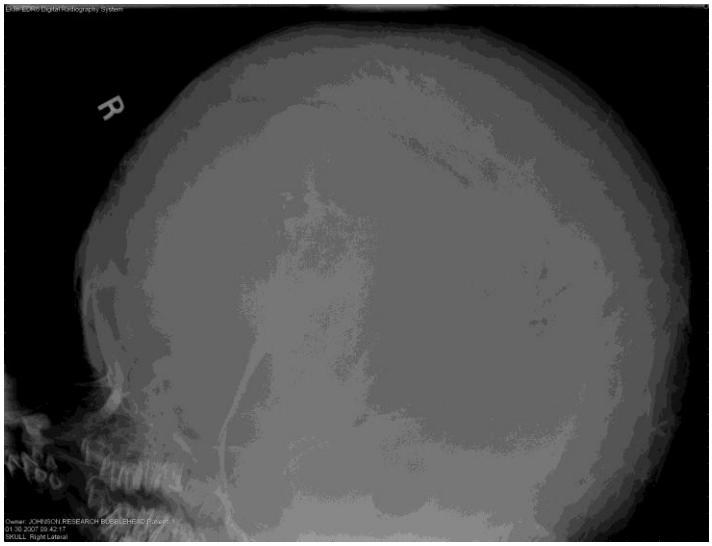

Figure 2. Neuropathic Hydrocephalus in a calf that was born dead. Notice the markedly enlarged cranium (A,B) and the loosely organized bones of malformed skull on the radiographic image (B). These images are courtesy of Dr. Brian K. Whitlock of The University of Tennessee.

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