Association Provides FCS Update

The following announcement was posted to *www.angus.org* Dec. 21. Check the web site to see if further updates have been posted since press time.

by ***American Angus Association***

At its November 2009 meeting in Louisville, Ky., the Board of Directors of the American Angus Association directed its professional staff to communicate directly with Dr. Jon Beever and Dr. David Steffen concerning the progress they were making in their ongoing efforts to deal with the syndrome previously identified as fawn calf syndrome (FCS). At the same meeting, the Board preliminarily agreed that it would generally process FCS carriers and their progeny in a fashion similar to the Association's handling of arthrogryposis multiplex (AM) and neuropathic hydrocephalus (NH) carriers and their progeny. The Board wanted to be comfortable that a test was commercially available before officially finalizing its approach to FCS.

The Association has now received and provides here the interim reports of Beever and Steffen. It will keep the membership apprised of any further developments as they occur.

Update from Steffen

The following update on FCS is provided by David Steffen, Veterinary Diagnostic Center, University of Nebraska–Lincoln.

Preliminary research done by Jon Beever (University of Illinois) supports Australian claims of recessive inheritance and a negative effect on productivity (personal communication) in animals with this syndrome. Muscle development is reported consistently poor in the affected calves that adapt. Severe cases have difficulty with locomotion and suckling and some die or are destroyed prematurely. Surviving calves are reportedly reproductively sound.

I have limited direct experience with this disorder as it is not lethal and, thus, few cases have been submitted for pathologic examination. The few I have seen were underperforming calves less than 6 months old. I have received several reports of affected calves with images demonstrating the characteristic "fawn" phenotype. I have referred my information to Dr. Beever so he can capture samples for molecular genetic studies.

Evidence suggests that this phenotype is inherited as a recessive trait, has a negative effect on performance and productivity and lies somewhere between *Heterochromia irides* and mule foot or dwarfism on the spectrum of undesirable traits in the breed.

Having a negative effect on productivity and being recognized as a simply inherited trait, I would advise the breed to continue research with the goal of identifying a test that will clearly demarcate the affected calves from any phenocopy and that can identify carrier cattle. Once developed, such a test would be used as a tool to eliminate the mutation from the breed.

At a minimum, once a test is available, it would be advisable to test at-risk high-impact animals and to require that the genotype data be shared with breeders so they can make informed herd management decisions regarding the trait.

Update from Beever

The following update on FCS is submitted by Jonathan Beever, University of Illinois.

With fall breeding season under way and no test for FCS yet available, it seems prudent to provide an update to the status of the FCS research project and attempt to provide answers to some frequently asked questions.

In review, data generated in 2004 by Australian researchers demonstrated the genetic control of FCS by embryo-transfer (ET) matings of putative carrier sires to affected females. These experimental matings produced calves affected with the previously described FCS pathology and in a proportion not inconsistent with recessive inheritance (i.e., affected individuals are expected to be homozygous for the mutation responsible).

Since Fall 2008, we have acquired DNA samples on more than 40 calves reported to have the FCS phenotype. Of these, only 27 calves were consistent with the pathology landmarks that we associate exclusively with FCS. In mid-Spring 2009, 17 of these FCS calves were genotyped using the high-density Illumina® BovineSNP50 Genotyping BeadChip, thus providing genotypes at more than 54,000 genetic markers for each individual. Analyses of this genotyping data demonstrated that all 17 affected calves shared a single chromosome segment and for which they were all homozygous. From these data, the clear conclusion is that the FCS phenotype is controlled by a single gene, and homozygosity is required for calves to be affected, clearly indicating a recessive mode of inheritance.

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In the April 2009 issue (see page 46), the *Angus Journal* published the Association's request for producers to report incidences of calves with phenotypes described as neuropathic hydrocephalus (NH) and fawn calf syndrome (FCS).

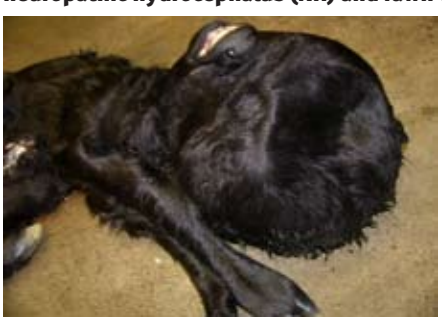

Fig. 1: Calf displaying hydrocephalus

Fig. 3: Calf displaying characteristics of FCS

Fig. 2: Calf displaying hydrocephalus

Fig. 4: Calf displaying characteristics of FCS

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Most recently, further results of the FCS breeding trial in Australia were reported by Dr. Laurence Denholm of the New South Wales Department of Industry and Development. In the 2008 breeding season, Denholm mated nine cows (those mature females that were produced in the 2004 trial) to their FCS-affected sibling bull. Of these nine cows, three were themselves FCS-affected and six were normal in phenotype, but obligate carriers of the FCS defect as they were produced by mating putative carrier bulls with affected cows.

The resulting calves from these 2008 matings were born this fall. All three FCS-affected females produced FCS-affected calves. For the six carrier cows, three produced normal calves and three produced FCS-affected calves. The results of these matings are again completely consistent with recessive inheritance of the FCS phenotype.

Based on these results, we have developed additional genetic markers within this chromosome segment and have used them, along with DNA from the remaining affected calves, to refine the position of the causative gene to a region of less than 2.4 million DNA base pairs. Within this region we have sequenced more than 40 candidate genes that we hypothesize could play a role in FCS if their function were compromised by a mutation. At this time, we believe that we have identified the gene causing FCS. Furthermore, we have been able to partially characterize the specific mutation responsible for FCS as a deletion of at least 35,000 DNA base pairs that removes a significant portion of this gene and would severely compromise its function.

So, why is there not a test for FCS if we know where and what the mutation is? The answer lies in the surrounding DNA sequence information. Although the cattle genome sequence is "complete" from a practical sense, there are still regions of the current genome assembly that are either incomplete or incorrect; this is the situation with the gene causing FCS.

By comparison with other species we can see that there are two problems with the current cattle genome sequence assemblies (there are two independent assemblies performed by different laboratory groups). On one side of the mutation, it would appear that both assemblies are missing roughly 15,000 base pairs of DNA sequence, indicating that these sequences may have never been generated (both assemblies are constructed from the same raw data by different methods). On the other side of the mutation, one assembly appears to be missing sequences (these sequences can be found in unassembled sequence databases) and the other appears to have several pieces "jumbled" in the incorrect order.

To rectify these issues, we have been generating de novo sequence from large DNA clones that we believe should contain the DNA sequences that are needed. We have generated more than 4.6 million base pairs of sequence information, representing more than a 12-fold redundancy of the region to be sequenced. To date, we have been unsuccessful at generating a complete assembly of this region. However, we have generated two contiguous DNA sequences that we believe contain the majority of the information that was previously missing. We are continuing to generate more sequence information and are beginning to use the new sequence that we have generated to better define the mutation.

In the meantime, we have often been asked if there are genetic markers that can predict an animal's FCS status with accuracy. In fact, it is true that as we develop additional genetic markers within this chromosome region and in this specific gene, some of these markers perform quite well at predicting an individual's genotype for FCS.

So why don't we release results that we have generated using these types of markers? Because we know these markers are not the specific mutation causing FCS, we know that they cannot, by definition, be 100% accurate. Additionally, because we only have a limited number of samples that have known genotype status for FCS, it is almost impossible to accurately assess the error rate of these markers. Thus, there is a significant danger of misuse/misinterpretation of these types of test results.

However, we can generate overall estimates of frequency of the FCS mutation in the population with these tests. Indeed, we have genotyped more than 500 animals with several of these genetic markers and estimate that the maximum frequency of FCS in the AI sire population will be around 3%-4%.

In summary, we are working as quickly as possible to get a 100% accurate test for FCS. We have made very significant progress towards achieving this goal; however, we have encountered a few roadblocks that have slowed us down considerably. We should have these issues reconciled shortly and look forward to finishing soon.

Editor's Note: *This technology is advancing rapidly and it is likely that newer information than the information reported above may be available by the time you receive your* Angus Journal. *Please monitor the Association web site at* www.angus.org *for the latest information available.*