

IMPORTANT UPDATE ON THE STATUS OF CURLY CALF SYNDROME

SUMMARY

On September 5, 2008, the American Angus Association posted a notice on its website (www.angus.org) in which it requested the assistance of its members and users of Angus genetics in obtaining reports of any abnormal calves believed to fit the accompanying description of what is currently described as “Curly Calf Syndrome”.

The following document includes:

- A notice from Dr. Jon Beever entitled “Likely Presence of Lethal Genetic Defect in a Specific Line of Angus Cattle”
- An Open Letter to the Membership from the Board of Directors
 - An introduction to the scientist, Dr. Beever, with whom the Association is working at this time
 - Primer on the basic science of genetics and how recessive genes are inherited
 - Discussion of how a diagnostic test is developed
 - Possible timetable for this situation

Between September 6 and September 15, 2008, the Association received written and verbal reports of 48 calves previously born dead with physical characteristics consistent with the Curly Calf Syndrome. Each report also included the recorded identities of the sire and dam of the abnormal calf. The Association has provided Dr. Beever with this information as it has become available. Based on the reports the Association has received since September 5, the following tentative conclusions appear likely:

- Curly Calf Syndrome appears to most likely be caused by a simple recessive gene, tentatively traced from the most recent common ancestor, GAR Precision 1680, Registration 11520398 (“1680”). This tentative conclusion does not preclude other ancestors of this bull, on either the sire or the dam side, from potentially being identified as carriers at a later time;
- Forty-seven of those 48 calves identified to the Association contained “1680” genetics on both sides of the abnormal calves’ pedigrees;
- With the assumption of a simple recessive inheritance pattern, the risk for producing a calf affected with this syndrome can manifest itself when the recessive gene is found in both the sire’s and dam’s pedigree.

As of yet, there does not appear to be any other mode of inheritance or reported environmental factors that explains this specific syndrome in these reported calves. As soon as Dr. Beever finds the mutation, he will turn to the important task of developing an accurate diagnostic test that will allow potentially impacted animals to be tested to determine if they are free of or are a carrier of this gene.

The Association urges every member to read this entire document carefully.

LIKELY PRESENCE OF LETHAL GENETIC DEFECT IN A SPECIFIC LINE OF ANGUS CATTLE

By Jonathan E. Beever, Ph.D.

On September 5, 2008, the American Angus Association posted a notice on its website (www.angus.org) in which it requested the assistance of its members and users of Angus genetics in obtaining reports of any abnormal calves believed to fit the accompanying description of what we are currently describing as “Curly Calf Syndrome.” Included within that posting was an article by Dr. Steffen, in which he presented two pictures of what the abnormal calves looked like.

Between September 6 and September 15, 2008, the Association received written and verbal reports of 48 calves previously born dead with physical characteristics consistent with this syndrome. Each report also included the recorded identities of the sire and dam of the abnormal calf. The Association has provided Dr. Steffen and me with this information as it has become available to them. While these reports have not yet resulted in DNA samples being taken from the calves’ parents and reviewed by me (although that effort is underway), I have determined that the following information should be publicized to the Association and its members.

Based on the reports the Association received between September 6 and September 15, 2008, the following tentative conclusions appear likely:

- Curly Calf Syndrome appears to most likely be caused by a simple recessive gene, tentatively traced from the most recent common ancestor, GAR Precision 1680, Registration 11520398 (“1680”). This tentative conclusion does not preclude other ancestors of this bull, on either the sire or the dam side, from potentially being identified as carriers at a later time;
- Forty-seven of those 48 calves identified to the Association contained “1680” genetics on both sides of the abnormal calves’ pedigrees;
- With the assumption of a simple recessive inheritance pattern, the risk for producing a calf affected with this syndrome can manifest itself when the recessive gene is found in both the sire’s and dam’s pedigree.

I continue to receive and process DNA that the Association is collecting and forwarding to me. But the evidence I have developed since September 5 is compelling. As of yet, there does not appear to be any other mode of inheritance or reported environmental factors that explains this specific syndrome in these reported calves.

As soon as I am certain that I have found the mutation, I will turn to the important task of developing an accurate diagnostic test that will allow potentially impacted animals to be tested to determine if they are free of or are a carrier of this gene.

In addition to continuing to report prior occurrences, the single most important thing a breeder can do to assist Dr. Steffen and me in this effort is to document any calf born with the previously-identified abnormalities by (1) taking a photograph of the calf, (2) retaining a tissue or whole blood sample (purple-top blood tube) from the affected calf and its dam, and (3) immediately contacting Don Laughlin, the Director of Member Services at the American Angus Association by e-mail (dlaughlin@angus.org) or at (816) 383-5140. Note: if possible, please retain the calf and Don Laughlin will make arrangements to have it shipped to Dr. David Steffen in Lincoln, Nebraska at the Association's expense.

AN OPEN LETTER TO THE MEMBERSHIP FROM THE BOARD OF DIRECTORS

We want to provide a thorough report to each of you as a result of the preliminary conclusions reached today by Dr. Jon Beever of the University of Illinois. While those conclusions are serious and should be taken seriously by all of us, they arrive against a backdrop of significant scientific advancements in the field of molecular genetics. That science has evolved to the point where we can now not only identify a recessive gene but also develop a test that can conclusively determine whether a suspect animal does – or does not – carry such a gene. This new reality separates us from our forefathers who were forced to abandon entire lines of cattle as the only way to deal effectively with the outbreak of dwarfism in the Angus and other breeds in the 1950s. There remains a need for caution, but we will meet this challenge by following an aggressive scientific plan of action that will allow us to continue industry leadership as a breed. This situation is and will continue to be monitored and dealt with by the Association and the scientists with whom we are now working. We intend to keep you abreast of any significant developments as they occur. Our goal has been and will continue to be one of transparency. By being transparent, we hope to avoid – or dramatically eliminate – the presence of false, baseless or misdirected rumor.

What we report below is done with the knowledge of Gardiner Angus Ranch. They have cooperated fully with the Association in its efforts to discern what we are dealing with.

Today, we want to introduce you to the scientist with whom we are fortunate enough to be working at this time. We next want to provide a primer on the basic science of genetics and how recessive genes are inherited. This will likely be a refresher course for you, but it bears repeating in situations such as the present one. We will turn then to how such a diagnostic test is developed and finally, offer a possible, but by no means certain, timetable for this situation.

The Scientists

In addition to its ongoing advisory relationship with David Steffen, DVM, Ph.D., of the University of Nebraska, the Association has been collaborating closely over the last month with Jon Beever, Ph.D., an Associate Professor of Molecular Genetics at the Department of Animal Sciences at the University of Illinois. That University has been heavily involved in developing both theoretical and applicable knowledge in genomic science and technology. With government funding, it began the Livestock Genome Sequencing Initiative some five years ago, the first step in mapping and sequencing cattle (and swine) genomes. Dr. Beever has played an instrumental role in isolating and identifying defective genes in at least three different breeds of cattle and, more importantly, in developing DNA tests for each that allow breeders to determine whether a suspect animal is free of the gene – or a carrier. His successes for those breeds in relatively short time frames have made him an important individual in our current situation. We are comforted by the fact that he is at work on this issue.

Dr. Beever has benefited from the notice published on our website on September 5. Because of your response, we have received detailed reports on 48 calves. But we continue to need such reports, especially if you have an affected calf during this fall calving season.

Before explaining where we are in this process, we turn first to a basic primer on genetics and the presence of recessives. This refresher will hopefully emphasize that armed with a test,

we can distinguish between animals free of this recessive gene from those who carry it. This will allow the unambiguous identification of large numbers of suspect-pedigree cattle that can be declared safe for use or continued use, thus retaining valuable germplasm from these cattle in the population.

A Look at Some Basic Genetics

At the outset, it is important to note that we have not yet amended the Rule 300 series to recognize the Curly Calf Syndrome as a Class I lethal genetic defect. We are awaiting the final determination from Dr. Beever. That said, to date, all “curly calves” tentatively have a most recent common ancestor of GAR Precision 1680, Registration 11520398 (“1680”). This knowledge allows breeders to make intelligent breeding decisions that will minimize the risk of having a curly calf. While certainly not all descendants of “1680” are carriers of the curly calf gene, until the mutation is identified and the DNA test developed, it will be difficult if not impossible to tell which animals are NOT carriers.

Based on this substantial pedigree evidence, there is compelling evidence to suggest that Curly Calf Syndrome is a genetic disorder inherited as a simple recessive trait. A recessive gene is one that you do not see in the offspring unless it is inherited from both parents. Thus, for a calf to be born with the abnormality, both parents must be carriers AND both parents must pass the curly calf gene to the calf. Perhaps the easiest way to understand the inheritance of curly calf is to compare it to how a black Angus cow and a black Angus bull can produce a red calf.

A dominant trait masks a recessive trait, so in the Angus world, black (dominant) masks red (recessive). What you see when you look at the animal is the “phenotype” – the physical characteristics – in our example the color of the animal. What you don’t see is the “genotype” – the genetic makeup of the animal. The genotype determines phenotype, or put differently the color genes determine the color of the animal. If an animal inherits the same color gene from both parents (both black or both red) it is called “homozygous” for that color. If an animal inherits 2 different color genes (1 black and 1 red) it is called “heterozygous” for the dominant trait, in this case heterozygous black.

So if we mate a black bull and a black cow we would not be surprised to have a black calf, but how is it possible to get a red calf? The calf inherits half its color genes from the bull and half from the cow. If the calf inherits a black gene from both parents it will be black in color – the phenotype is a black calf and the genotype is homozygous black. If the calf inherits one black gene and one red gene it will also be black in color (black masks red) but the genotype will be heterozygous black. If the calf inherits 2 recessive red genes, it will be red in color – red phenotype and homozygous red genotype. With heterozygous black parents (1 black and 1 red gene) the calf could have 1 of 3 different genotypes.

The Punnett square (Figure 1) shows the 3 possible genotypes of a calf when both parents are heterozygous black. The Punnett square also shows the probability of inheriting a specific trait. Big “B” is black and dominant. Little “b” is red and recessive. The bull in this example can contribute either a dominant black gene (B) or a recessive red gene (b). The cow in this example can also contribute either a black or red gene. How the combination of genes comes together in the calf determines the genotype and consequently the phenotype. Every time this pair is mated there is a 75% chance that the calf will be black (BB or Bb) in color and 25% chance it will be

red (bb). However, there is a 50% chance that the calf will carry the recessive red gene (heterozygous black = Bb).

| Figure 1 | Genotype of bull | |
|-----------------|------------------|----|
| Genotype of cow | B | b |
| B | BB | Bb |
| b | Bb | bb |

Figure 1: Possible genotypes and the probability of inheriting a specific color when a heterozygous black bull (Bb) is mated to a heterozygous black cow (Bb). B = dominant black and b = recessive red. Note that 3 of 4 calves will be born black in color (BB, Bb & Bb) and 1 of 4 will be born red (bb). Two of 3 black calves will carry the recessive red gene. The red calf is an example of inheritance of a recessive trait.

The same principles apply to the inheritance of curly calf (Figure 2). In this example big “C” is normal and dominant, while little “c” is the recessive mutation for curly calf. Note that not all offspring of “1680” have the recessive gene in their genotype. In fact, as you can see from the description of inheritance of the recessive red gene, only 50% of direct offspring can be carriers of the recessive curly calf gene. So each time 2 carriers (Cc) are mated there is a 50% risk of producing a carrier (Cc), a 25% chance of producing a “normal” calf (CC) and a 25% risk of having a curly calf (cc). The transmission of any recessive genetic defect is exactly like getting a red calf from heterozygous black Angus parents.

| Figure 2 | Genotype of bull | |
|-----------------|------------------|----|
| Genotype of cow | C | c |
| C | CC | Cc |
| c | Cc | cc |

Figure 2: Possible genotypes and the probability of inheriting the curly calf gene when a curly calf carrier bull (Cc) is mated to a curly calf carrier cow (Cc). C = dominant normal gene and c = recessive curly calf gene. Note that 3 of 4 calves will be “normal” looking (CC, Cc & Cc) and 1 of 4 will be a curly calf (cc). When mating two carriers of the curly calf gene, half of the offspring will be carriers for the lethal defect (Cc).

Now if the chance for a normal calf is 25% and the risk of a carrier calf is 50%, does this mean that the fourth time you breed this carrier cow and this carrier bull you will have a curly calf? NO, absolutely not. The risk of having an affected calf is 1 in 4 every single time you mate 2 carriers. It is like flipping a coin – the chance of getting heads is 50% every time you flip the coin. Even though you may get several heads in a row, the chance that you get heads on the next flip is 50%. So for a coin flip the laws of probability tell us for 100 flips, 50 will be heads and 50 will be tails. Similarly, if you mate a carrier bull to 100 carrier females, 25 will have Curly Calf Syndrome, 50 will be carriers, and 25 will be normal. Although it is often difficult to see this ratio in herds of smaller size, the risks are the same every time you mate a carrier to a carrier.

There is another scenario that can come into play here, and that is breeding a carrier to a “clean” animal (Figure 3). If we look at the black–red example, it is the same as breeding a homozygous black cow (BB) to a black bull carrying the red gene (Bb) – all the calves will be black but half will be heterozygous black and carry the red gene. In the case of curly calf, breeding a “normal” cow (CC) to a carrier bull (Cc) results in all calves appearing “normal” but 50% will carry the gene for curly calf. The same is true for breeding a carrier cow to a “normal” bull – all calves will appear “normal” but half will carry the gene for curly calf.

| | | |
|------------------------|-------------------------|-----------|
| Figure 3 | Genotype of bull | |
| Genotype of cow | C | c |
| C | CC | Cc |
| C | CC | Cc |

Figure 3: Possible genotypes and the probability of inheriting the curly calf gene when a curly calf carrier bull (Cc) is mated to a clean cow (CC). C = dominant normal gene and c = recessive curly calf gene. Note that all calves will be “normal” looking (CC, CC, Cc, & Cc). When mating a curly calf carrier to a clean animal, half of the offspring will be carriers for the lethal defect (Cc).

So how can you make intelligent breeding decisions if there is no test yet for curly calf? We understand that Curly Calf Syndrome appears to most likely be caused by a simple recessive gene, tentatively traced to the most recent common ancestor, “1680”, suggesting that “1680” is a carrier for the curly calf gene. Because we understand the inheritance of recessive traits we also know that some, but not all, of his direct offspring are carriers for curly calf. Generally, the laws of probability would say that out of 100 offspring, 50 would be “normal” and 50 would be carriers, but until there is a test we don’t know which animals are “free” of the defect. If we know that all affected calves to date have traced to “1680” on both sides of their pedigrees, then it stands to reason that breeders increase the risk of having a curly calf if they mate animals with “1680” in their pedigree to other animals with “1680” also in their pedigree.

The Timetable

Dr. Beever has made significant strides already in putting together pedigrees of a number of abnormal calves and their ancestors. He believes that he may only need several more animals from the candidate population before he is able to identify and isolate – by the use of markers – that region in which the potential gene is located. Once that region is isolated, he will then turn to the task of locating the actual gene responsible for the syndrome. The identification of the specific gene leads in fairly quick order to the development of a test for identifying the presence or absence of that gene in any animal. Thereafter, a protocol is developed that can be followed by participating labs authorized to perform the test on DNA from potential carriers.

It is not possible to put a precise timeframe before you because, in fairness to Dr. Beever, he remains several animals short of the number he would like to have. The search for the actual gene could take as little as 90 days from the date he is satisfied with the number of animals he is looking at to as long as six months. Thus, we wish to reemphasize the need for prompt reporting of animals, so that DNA samples can be collected as soon as possible, so as to not delay the process.

We are hoping that the gene can be located by Thanksgiving and that qualified labs could begin to accept DNA and test potential carriers as early as February 2009. That is our goal. We will keep you informed as we proceed.

Conclusion

We will continue to monitor this situation closely and report on Dr. Beever’s progress to you. We believe that the steps we have taken are proactive and will strengthen our breed.

The Officers and the Board of Directors