Research Update on Hydrocephalus

By Jonathan E. Beever, Ph.D.

Earlier this year the American Angus Association, via Dr. Steffen at the University of Nebraska-Lincoln, posted a request for reporting of calves having a phenotype referred to as hydrocephalus. As Dr. Steffen described in the request, these calves have a severe phenotype that includes an extremely large cranium with little or no brain and spinal cord present. Prior to the posting of this request, 15 calves matching this phenotype had been submitted. Since that request, there has been continued reporting of additional calves. It was previously unclear whether the condition had a genetic or environmental basis; however, pedigree analysis of these calves did show common ancestry on both sides of their pedigrees. This was not interpreted as clear evidence of a genetic defect as we believed that this pedigree relationship may have been caused by biased reporting of calves related to pedigrees associated with the arthrogryposis multiplex (AM) defect that had been requested in September 2008.

Using DNA from the reported calves, we performed an analysis in late February 2009 to assess a potential molecular basis of this condition. Based on this analysis, we are able to confirm that this defect is the result of homozygosity at a distinct location on a single cattle chromosome; thus confirming that the condition was caused by a recessive mutation. Since that time, we have continued to investigate this chromosomal region in an effort to identify the specific mutation and develop a DNA-based test to identify carriers of the defect.

We are happy to report that a mutation has been identified that we believe is the cause of this abnormality. This mutation resides within a gene that is involved in development and maintenance of central nervous system tissue. The gene is highly conserved across species as would be expected given its role. Within this gene are several regions that encode parts of the protein with catalytic function. The mutation we have identified is the change of a single DNA base pair. As a result of this change, the encoded protein is also changed at a single amino acid that is highly important in one of these functional regions of the protein. Based on comparison of this change across multiple species from the fruit fly to higher primates, such as humans, this change is classified as “intolerable” or “severely damaging” to protein function. Furthermore, mutations within this gene for species such as the mouse also cause severe abnormalities including high (nearly 100%) embryonic mortality rate.

Similar to the work that was performed for AM, we have had the opportunity to test more than 1,000 DNA samples for this mutation. To date, there have been no living animals identified that are homozygous for this mutation (i.e., have the mutation on both chromosomes). This strongly supports the conclusion that homozygosity for this mutation is incompatible with life and is the causative mutation in this defect. In contrast, all calves that have been diagnosed with this form of hydrocephalus have genotyped as homozygous for this mutation. Additionally, we have identified the common ancestor from which the mutation originated and can confirm that this ancestor is represented on both sides of the pedigrees of all affected calves with DNA samples submitted to date. Therefore, we believe that genotyping individuals for this specific mutation will accurately provide classification regarding this genetic defect.

As we come to the conclusion of this research, we again will be able to provide genotype status on AI sires that were submitted for the AM research. We expect that we will complete the genotyping of these sires by the end of this week and will be ready to release these results in coordination with the American Angus Association and the National Association of Animal Breeders beef committee. In the next couple of weeks we will also aim to move this technology into commercial testing facilities so that at risk animals can be tested.