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Angus Dwarfism: The Short Story about ISU’s Discovery of a Causal Mutation for Dwarfism in American Angus

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Angus Dwarfism: The Short Story about ISU’s Discovery of a Causal Mutation for Dwarfism in American Angus

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Summary and Implications

Angus dwarfism has been localized to bovine chromosome 6 (BTA6) by linkage mapping. Four positional candidate genes suspected to alter bone development have been identified and are under analysis. A causative mutation was found in the PRKG2 gene. Subsequently, a genetic test was developed so that Angus breeders may select against dwarfism. This test successfully predicted which calves were dwarves with 100% accuracy in a breeding experiment recently concluded at Iowa State. Preliminary data in cell culture indicates that the mutation discovered changes the function of the PRKG2 gene, strongly suggesting it is the causative mutation in American Angus.

Materials and Methods

A pedigree of 23 individuals was assembled to follow the relationship between six confirmed Angus dwarves. Microsatellite markers were genotyped across a panel of bovine chromosomes and analyzed using a maximum likelihood method based upon the Elston-Steward algorithm. For each marker interval, a likelihood of odds (LOD) score was calculated to determine the statistical association between the given marker interval and the dwarfism phenotype. The LOD score was calculated as the log base 10 of the likelihood ratio of (L1/L2) assuming: 1) the dwarf gene is at the center of the flanking markers (L1), and 2) the dwarf gene is on another chromosome (L2). We rejected the null hypothesis that the dwarf gene is on another chromosome when the LOD score was greater than 3 (P<0.001). Based upon the initial analysis, we detected linkage of dwarfism to the telomeric end of BTA6 (LOD=6.89). Nineteen additional microsatellite markers were genotyped within this region to further narrow our search for the dwarf mutation within a 2.8 centiMorgan (cM) region (LOD=7.88). We focused on 0.8cM of this region where the LOD score was maximal. Polymerase chain reaction (PCR) was used to amplify four candidate genes within this region. Single nucleotide polymorphisms (SNPs) were discovered by sequencing these PCR amplicons. The SNPs were genotyped using restriction fragment length polymorphism (RFLP) analysis and single base primer extension. Association of SNPs to dwarfism was assessed as previously described.

Results and Discussion

Analysis within and surrounding candidate genes suggested a region of 0.49cM containing the mutation (LOD=8.64) (Figure 2). The region of interest contained the PRKG2 gene, which is known to harbor mutations causing dwarfism in the mouse and rat. Additional testing has verified that this mutation is 100% concordant with dwarf carriers and dwarves. Embryo transfer was used to breed a known dwarf carrier with another carrier and a dwarf cow. Six calves were produced, 4 dwarves and 2 unaffected animals. The genetic test developed to find the PRKG2 mutation correctly predicted which animals were normal or dwarves at birth. Concurrently, we tested the functionality of the dwarf PRKG2 mutation in cell culture. Preliminary results indicate that the PRKG2 mutation change the level of collagen 2 (COL2) gene expression by greater than 60% (p<0.01). Since proper COL2 expression is vital to the growth and maturation of long bones, this is believed to severally alter bone growth, likely leading to dwarfism. Therefore, we believe this mutation is causative for dwarfism in American Angus cattle. Future research will.
focus on understanding how the PRKG2 mutation alters the physiology of dwarf cattle, with potential implications to human medicine. After many years, a genetic test will finally be made available to producers in the near future.

Figure 2. Linkage analysis of Angus dwarfism to SNPs on BTA6.