Homozygosity Mapping Approach for the Chondrodysplasia Gene in Dexter Cattle

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Dexter cattle are a popular breed in Australia, but are often discriminated against, as they are known to be carrying a lethal genetic defect, chondrodysplasia. The affected fetuses display disproportionate dwarfism, a short vertebral column, marked micromelia, a relatively large head with a retruded muzzle, cleft palate and protruding tongue and a large abdominal hernia. It appears that two A.I. sires carrying the defect have been excessively used in Australia with a number of "bulldog" calves produced, and an estimated minimum heterozygote frequency calculated at 19% (Harper et al., 1998). There is considerable evidence to support the view that chondrodysplasia is inherited in an incompletely dominant manner, i.e. the carrier animal may look shorter in the leg than a normal animal. Symes (1981) conducted an experiment in which physical size measurements of animals were recorded to predict the carrier status of the animal. Nicholas et al. (1996) analysed the measurement data and concluded that it has potential to identify non-carriers, but is not an accurate test. A DNA-test would be accurate, and easy for breeders, as hair samples can be used for the test, but it requires the disease-causing mutation to be identified. We are using a homozygosity mapping approach to the problem (Charlier et al., 1996), combined with candidate-gene selection, which is an efficient method to find the gene responsible for chondrodysplasia.

DNA samples were collected from "bulldogs", parents of "bulldogs", other relatives of "bulldogs", and distantly-related animals (controls). Presuming validity of the mode of inheritance, DNA parentage verification of the "bulldog" fetuses confirmed the sires and dams of these fetuses as obligate carriers of chondrodysplasia.

Twelve candidate genes were identified by searching for diseases in humans and mice in which a similar phenotype to Dexter "bulldogs" was described. It is possible that a mutation in one of these genes may cause chondrodysplasia in Dexters. Using comparative mapping, nine regions on the cattle genome homologous to the candidate genes were identified. 90 microsatellite markers were selected to cover these regions. Genotyping was performed using 22 animals including 11 parents or grandparents, 8 "bulldog" samples, and 3 distantly related animals to act as controls. The genotype data were analysed for regions of homozygosity amongst the affected samples. We would expect DNA markers adjacent to the disease causing mutation to show homozygosity in affected animals, whereas carriers or unaffected animals will show heterozygosity.

There have been 70 markers genotyped to date. By visual examination, only one of these markers (marker A) shows a homozygous pattern amongst 5 of the 8 "bulldogs", and yet a variety of alleles amongst the parents and controls. CRI-MAP (Green et al., 1990) was used to estimate recombination frequencies between markers and the chondrodysplasia locus: marker A gave a positive LOD score of 2.11, as did an adjacent marker B (3.3cM from A), which was analysed after the initial screen. Although the LOD score of 2.11 is not statistically significant, these preliminary results justify further investigation of this region. To confirm these initial results, more samples from relatives are currently being collected and genotyped.

A candidate gene located close to marker A is currently being screened for disease-causing mutations. If a mutation is found, DNA-based testing will allow identification of carrier animals. Dexter breeders all over the world will benefit from an accurate DNA test, as they will be able to prevent carrier/carrier matings, thus eliminating the occurrence of "bulldogs" and providing a valid methodology for genetic improvement of the breed that does not depend on exploitation of a gene(s) associated with a genetic defect.

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