

## **THE STUDY OF THE GENETICS OF CRANIAL CRUCIATE LIGAMENT RUPTURE IN THE DOG**

Rupture of the cranial cruciate ligament (CCLR) in the dog is the most common cause of hind limb lameness. When CCLR occurs it results in instability in the knee leading to progressive, debilitating arthritis and lameness. Particular breeds of dogs (e.g. Newfoundland, Rottweiler) are predisposed to CCLR while other breeds (e.g. Greyhound) have dramatically reduced frequency of this disorder. These breed differences support a genetic cause for the CCLR trait.

For this study, we have thus far performed four steps toward understanding the underlying genetic basis for CCLR. In the first step, we wanted to establish the overall economic impact to veterinary clients for the medical and surgical management for CCLR; the estimate was \$1.3 billion in the U.S. for the year 2003. Next, we established the prevalence rate for CCLR in a hospital population of Newfoundlands and examined a recruited pedigree of Newfoundlands for potential mode of inheritance for CCLR. Medical records were examined for a diagnosis of CCLR for all Newfoundlands that presented to the Iowa State University Veterinary Teaching Hospital.

One hundred sixty three Newfoundlands were evaluated from January 1, 1996, through December 31, 2002, and 22% were diagnosed with CCLR. In addition, a large-scale recruitment study was undertaken from the National Newfoundland Registry and local breeders and included 411 Newfoundlands, of which 92 (22%; 53 females and 39 males) were affected with CCLR and 319 (182 females and 137 males) were unaffected. Analysis of this recruited population of Newfoundlands revealed the average inbreeding coefficient for those animals that were inbred was 0.05 (range 0.004 – 0.17), that heritability for CCLR was 0.27, and the complex statistical analysis predicted a recessive pattern of inheritance. The frequency of the recessive allele was 0.60 with 51% penetrance meaning that of the expect 36% of the population that was expected to display the disorder only about half of them would show signs of CCLR.

A third step was to evaluate biological candidate genes (genes selected for analysis because they may play a role in the cause of CCLR) for an association to the CCLR trait. Analysis yielded single nucleotide polymorphisms (SNPs) in several genes, but association analyses, performed on 90 dogs selected from a population of Newfoundlands; 45 unaffected and 45 affected with CCLR, revealed no statistically significant association with the genes and CCLR status. The fourth step in this study was a genome scan which utilized 417 microsatellite markers (MSAT) well spaced along the dog genome. Initial results indicated CCLR status was possibly linked to seven chromosomes that had 4 or more markers with statistical significance. These were chromosomes 3, 5, 10, 14, 18, 23, and 27. Fine mapping these chromosomal regions should further narrow the list of potential CCLR candidate genes. Our efforts are continuing to pursue these leads with the eventual goal of developing a genetic test to determine animals more likely to be susceptible to this disorder.

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