RESEARCH PROGRESS REPORT SUMMARY

Grant 01312: Association mapping study of Legg-Calve-Perthes Disease in the West Highland White Terrier, Yorkshire Terrier, and Cairn Terriers

Principal Investigator: Dr. Alison Starr-Moss, PhD

Research Institution: Clemson University

Grant Amount: $78,688.00

Start Date: 1/1/2010 **End Date:** 6/30/2013

Progress Report: FINAL

Report Due: 6/30/2013 **Report Received:** 6/18/2014

Recommended for Approval: Approved

(Content of this report is not confidential. A grant sponsor's CHF Health Liaison may request the confidential scientific report submitted by the investigator by contacting the CHF office. The below Report to Grant Sponsors from Investigator can be used in communications with your club members.)

Original Project Description:

Background: Legg-Calve-Perthes Disease (LCPD) is a debilitating developmental disease that affects small breeds of dog, particularly terrier breeds. The only outward indications of this condition are pain, lameness, and muscle atrophy of the hip joint. These signs are not exclusive to LCPD, and are often attributed to minor trauma during the early stages of disease. LCPD is primarily diagnosed by radiographic changes of the femoral head within the hip joint. Due to the developmental nature and the unknown etiology of the disease, LCPD is difficult to predict and prevent. No disease mapping strategies have been employed to date.

Objective: This study is using the Affymetrix canine single nucleotide polymorphism (SNP) chip to identify regions that are linked to LCPD in the West Highland White Terrier, Yorkshire Terrier, and Cairn Terrier breeds.

Grant Objectives:

Objective 1: Sample collection and phenotype confirmation. Collect a total of 200 samples with a minimum of 50 per breed.

Objective 2: Probe SNP array for genome wide association

Publications:

Starr-Moss AN, Nowend KL, Alling KM, Zepp EJ, Murphy KE (2011) Exclusion of COL2A1 in canine Legg-Calvé-Perthes disease. Animal Genetics. doi:10.1111/j.1365-2052.2011.02215.x

Additional manuscript in preparation.

Report to Grant Sponsor from Investigator:

Legg-Calvé-Perthes Disease (LCPD) is a developmental orthopedic disorder of the coxofemoral joint that is observed in humans and dogs. A loss of vasculature in the developing femoral head leads to necrosis and subsequent microfracture of the capital femoral epiphysis. The resultant articular incongruency reduces joint stability and can cause secondary osteoarthritis. LCPD is among the most common hip disorders diagnosed in children. In humans, private mutations have been identified in COL2a1, but sequencing in dogs did not reveal any causative mutations (Starr- Moss et al. 2012). The etiology of LCPD remains poorly understood, and genetic and environmental factors are expected to play a role in the disease. LCPD most commonly affects breeds of small stature, including the West Highland white terrier (WHWT), Yorkshire terrier (YT), Cairn terrier (CT), schipperke (SCH), and poodle (PDL). A multi-breed genome-wide association study was undertaken to identify loci contributing to canine LCPD.

This study aimed to identify genomic regions associated with Legg-Calve-Perthes Disease (LCPD) in terrier breeds, including West Highland White Terriers (WHWT), Yorkshire Terriers, and Cairn Terriers. To this end, we have completed a genetic study using a population of 129 dogs (51 LCPD-affected, 78 control). Optimally, we hoped to identify a major locus causing LCPD in dogs, and identify a marker that could be reliably used to predict and prevent cases of LCPD.

Our initial goal was to collect blood samples from 200 dogs of the three aforementioned breeds; however, insufficient numbers of study participants were obtained. Two additional breeds, Schipperkes and Fox Terriers, significantly increased the numbers of study participants; seven additional breeds submitted <5 samples. In total, samples from 205 dogs were submitted to our laboratory for this work. From these samples, 163 genetic profiles were generated. Our methods were changed midway through this grant period to produce better quality data. While 163 genetic profiles were generated, 39 samples were repeated between the two methods.

LCPD has been proposed to be an autosomal recessive disease. Our study results do not support this hypothesis. LCPD appears to be genetically complex, likely with several genes contributing to the onset of clinical signs.

The analyses of our data did not reveal a major locus shared among the breeds that could explain the onset of LCPD. Individual regions identified from the analyses are being examined further for genotypes that are highly correlated with LCPD and that may be used as predictors of LCPD. There are no immediate candidate genes to sequence, nor is there a test at this time to avoid producing LCPD. One candidate gene identified from human cases of LCPD, COL2A1, was sequenced in affected and control WHWT and excluded as being involved in canine LCPD. Additional analyses with new software programs are being carried out. It is our hope that these secondary analyses will help dissect the complex genetic control of LCPD. Further work remains necessary to elucidate these mechanisms.

Importantly, however, it appears as though there are subclinical LCPD-affected dogs in terrier populations. As samples were collected for this study, a family of fox terriers with three LCPD affected members was identified and recruited for study participation. Two of the three affected dogs shared a sire, but occurred in different litters with unrelated dams. After radiographing the littermates and parents of these affected dogs, four additional LCPD-affected dogs were diagnosed, based on characteristic hip changes. In this family, the percentage of affected dogs increased from 12% to 32% after detailed radiographic examination. The 4 previously unknown LCPD dogs had no history of trauma or limping. A manuscript is in preparation describing this family of fox terriers, and recommending the radiographic evaluation of dogs with LCPD relatives, even in the absence of clinical signs.