



RESEARCH PROGRESS REPORT SUMMARY

Grant 01311: Genome-wide association mapping study of hypertrophic osteodystrophy in Irish Setters

Principal Investigator: Dr. Alison Starr-Moss, PhD

Research Institution: Clemson University

Grant Amount: \$74,237.00

Start Date: 1/1/2010 **End Date:** 6/30/2014

Progress Report: FINAL

Report Due: 6/30/2014 **Report Received:** 4/17/2015

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: Hypertrophic osteodystrophy (HOD) is a debilitating, metabolic bone disease that, in mild cases, can lead to deformation of mature bone, and in severe cases, can require euthanasia of affected dogs. At present, the cause of HOD is unknown. Most cases of HOD are observed shortly after vaccinations, the most often proposed causes are distemper virus infection, post-vaccination infection, bacterial infection, or other viral infections. The predominance of HOD in several breeds of dog suggests a heritable component of the disease. Due to the complex nature of the immune system and its many components, analysis of candidate genes would have to be exhaustive.

Objective: The researchers aim to identify genes involved in HOD with the whole genome association mapping using the canine single nucleotide polymorphism (SNP) chip. This resource will identify regions exhibiting linkage with HOD. Such regions will then be assessed for gene(s) involved in the disease.



Grant Objectives:

Objective 1: Sample collection and phenotype confirmation. Collect a total of 200 samples.

Objective 2: Probe SNP array for genome wide association.

Publications:

Rinz CJ, Levine J, Minor KM, Humphries HD, Lara R, Starr-Moss AN, Guo LT, Shelton GD, Clark LA. (2014) A COLQ missense mutation in Labrador Retrievers having congenital myasthenic syndrome. PLoSOne. 9(8):e106425.

Report to Grant Sponsor from Investigator:

Hypertrophic osteodystrophy (HOD) is a complex disorder of the musculoskeletal and inflammatory systems in dogs. HOD has been recognized as an animal model of chronic recurrent multifocal osteomyelitis (CRMO). In humans, mutations causing CRMO have been described in the genes LPIN2 and IL1RN. A mouse model of CRMO results from defects of *pstpip2*. Defects of any of these genes results in syndromic forms of CRMO, and the disease affects multiple body systems. The etiology of HOD remains poorly understood, and genetic and environmental factors are expected to play a role in the disease. HOD commonly affects breeds of large stature, including the Irish Setter, Great Dane, and Weimaraner. A genome-wide association study was undertaken to identify genes contributing to HOD.

The primary aim of this study was to identify genes associated with HOD in Irish Setters. To this end, we completed a genomic study using a population of 89 dogs (40 affected, 49 control). Optimally, we hoped to identify a major locus contributing to HOD in dogs, and identify a genetic marker that could be reliably used to predict and prevent cases of HOD.

Our initial goal was to collect blood samples from 200 Irish Setters; however, insufficient numbers of study participants were obtained. We modified our aims to complete the genetic screen with fewer dogs, while adding a new aim: whole genome re-sequencing from healthy and HOD-affected Irish Setters. We planned to have whole genome sequence augment the data generated from the genomic screen. We were able to generate whole genome sequence for three Irish Setters: 2 HOD-affected, and 1 healthy. Using the boxer reference as a control, as well as data from several other breeds from our laboratory, we were able to compare the coding sequence in regions identified by the genomic screen and CRMO candidate genes in HOD-affected dogs to healthy dogs. Several variants were detected and are currently being investigated further.



The combination of two whole-genome approaches did not yield a major locus contributing to HOD in Irish Setters. Two genomic regions appear interesting, but further research is needed to understand the genetic contribution to the onset of HOD. The availability of whole-genome sequence will allow for immediate assessment of candidate genes identified from the genomic screen and/or future studies. There is no test at this time that can reliably detect HOD risk alleles. 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 HOD. Further work remains necessary to elucidate these mechanisms.