GRANT PROGRESS REPORT REVIEW

Grant: 00757A: *Hereditary Mutations in Genes Associated with Osteosarcoma in Large Dog Breeds*

Principal Investigator: Dr. Kerstin Lindblad-Toh, PhD

Research Institution: Broad Institute

Grant Amount: $91,481.04

Start Date: 4/1/2007 **End Date:** 9/30/2009

Progress Report: 30 month

Report Due: 9/30/2009 **Report Received:** 9/30/2009

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.)

Original Project Description:
Background: Osteosarcoma (OSA), bone cancer, affects 8,000 - 10,000 dogs in the United States annually. Large and giant breeds are at a much higher risk for this disease, suggesting that inherited risk factors are involved. Roughly 10 - 15 percent of Rottweilers, a mastiff-type breed and 15 - 20 percent of Greyhounds, a long-limbed hound-type breed, get the disease. Recently, researchers have identified several regions of the canine genome that are associated with an increased risk for OSA in Rottweilers. A similar study is underway for Greyhounds and is expected to identify additional regions of importance.

Objective: The study aims to identify the actual genes and mutations causing the increased risk for bone cancer in Rottweilers and Greyhounds. The researchers will then determine the frequency of gene mutations in OSA for other breeds as well as in other tumors. This work should allow the development of specific genetic tests for carriers of OSA and suggest further studies leading to improved treatments for bone cancer.

Original Grant Objectives:
Objective 1: To fine-map the regions of OSA association in Rottweilers and Greyhounds

Objective 2: To identify disease-associated mutations in genes in OSA associated regions

Objective 3: To assess whether the same mutations/genes are associated with OSA in additional breeds and with other types of cancers

Publications:

Karlsson EK, Baranowska I, Wade CM,, Salmon Hillbertz NHC, Zody MC, Andersson N, Biagi T, Patterson N, Rosengren Pielberg G, Kulbokas EJ III, Comstock KE, Keller ET, von Euler H, Kämpe O, Hedhammar A, Lander ES,, Andersson G, Andersson L, & Lindblad-Toh K Efficient mapping of mendelian traits in dogs through genome-wide association (2007) Nat Genet. 2007 Nov;39(11):1321-8.

Report to Grant Sponsor from Investigator:

In our completed CHF study "Mapping Genes Associated with OSA in Large Breed Dogs", we have identified genomic regions associated with OSA in Rottweilers and Greyhounds using genome-wide association with the newly developed ~27,000 SNP array. Results of genome-wide scans show that three regions are associated with OSA from the genome-wide screen in Rottweilers and three different and non-overlapping regions are associated with OSA in Greyhounds. In this study, we have proposed to conduct further fine-mapping of these candidate regions using additional Rottweiler samples paired with Mastiff-type breeds (Golden Retrievers and Leonbergers) and, likewise, additional Greyhound samples paired with Long-limbed Hound type breeds (Irish Wolfhounds and Great Danes). We have now performed fine-mapping in ninebreed. All six loci are supported, and several candidate genes have been interrogated for mutations. Since no coding candidate mutations have been identified so far, we believe that regional resequencing will be necessary and the methodology to do this has been developed. We have also continued to fine-map in larger sample numbers to identify the most highly associated regions in preparation for regional resequencing to identify mutations. Regional resequencing is now ongoing to identify mutations.

Rottweiler Health Liaison:

Osteosarcoma (OSA), or bone cancer, affects 8,000-10,000 dogs in the United States annually. Large and giant breeds are at a much higher risk for this disease, suggesting that inherited risk factors are involved. The purpose of this study is to identify the mutations causing the increased risk for bone cancer in Rottweilers and Greyhounds. To do this, we have proposed to compare the genotypes of dogs diagnosed with OSA with healthy older dogs using a statistical analysis. To date, we have collected ~500 blood samples from dogs diagnosed with OSA and ~1500 healthy dogs over 8 years old. Of these, we have collected 87 blood samples from Rottweilers diagnosed with OSA and 85 healthy Rottweilers over 8 years old. We have localized genetic risk factors that are associated with OSA to three chromosomal regions in Rottweilers and are currently narrowing in on the precise mutations that cause the disease. The biological effects of the mutations will be studied to better understand the cause and progression of the disease. This work should allow the development of specific genetic tests for carriers of OSA and suggest improved treatments for OSA.

Greyhound Health Liaison

Osteosarcoma (OSA), or bone cancer, affects 8,000-10,000 dogs in the United States annually. Large and giant breeds are at a much higher risk for this disease, suggesting that inherited risk factors are involved. The purpose of this study is to identify the mutations causing the increased risk for bone cancer in Rottweilers and Greyhounds. To do this, we have proposed to compare the genotypes of dogs diagnosed with OSA to healthy older dogs using a statistical analysis. To

date, we have collected ~500 blood samples from dogs diagnosed with OSA and ~1500 healthy dogs over 8 years old. Of these, we have collected 171 blood samples from Greyhounds diagnosed with OSA and 276 healthy Greyhounds over 8 years old. We have localized genetic risk factors that are associated with OSA to three chromosomal regions in Greyhounds and are currently narrowing in on the precise mutations that cause the disease. The biological effects of the mutations will be studied to better understand the cause and progression of the disease. This work should allow the development of specific genetic tests for carriers of OSA and suggest improved treatments for OSA.