RESEARCH PROGRESS REPORT SUMMARY

Grant 01766: Identification and Validation of the Genes That Define Abnormal Development of the Kidney in Dogs

Principal Investigator: Dr. Kerstin Lindblad-Toh, PhD

Research Institution: Broad Institute

Grant Amount: $25,000.00

Start Date: 1/1/2013 **End Date:** 12/31/2014

Progress Report: End-Year 1

Report Due: 12/31/2013 **Report Received:** 1/3/2014

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:

Renal dysplasia occurs in many breeds and an increased prevalence in certain breeds suggests a genetic influence. Identification of the genetic cause in dogs is essential as there is no treatment and affected dogs progress to renal failure and death at a young age. Despite prior candidate gene studies, the genetic cause of canine renal dysplasia in various breeds remains unclear. It is unknown if the same gene is affected in all breeds with renal dysplasia or if different genetic variants exist in each breed.

We recently conducted a genome-wide association study in Boxers with renal dysplasia. The analysis suggests an association to an excellent candidate gene. Here we propose genetic and functional studies to identify the causative mutation in Boxers. We also propose to collect additional samples from Boxers and other breeds affected by renal dysplasia, focusing on Miniature Schnauzers, Lhasa Apsos, Shetland Sheepdogs, and Soft Coated Wheaten Terriers. Additional genome-wide association studies in Boxers and other breeds will help us dissect the genetics of canine renal dysplasia, improve our understanding of renal development in dogs and humans, and determine whether breed specific genetic tests will be required for prevention.

Grant Objectives:

Aim 1. Mutation detection in the associated Boxer risk locus with functional analysis of selected variants.

Aim 2. Collection of additional samples from dogs with renal dysplasia and old healthy dogs.

Publications:

None at this time.

Report to Grant Sponsor from Investigator:

Renal dysplasia occurs in many breeds and an increased prevalence in certain breeds suggests a genetic influence. Identification of the genetic cause in dogs is essential as there is no treatment and affected dogs progress to renal failure and death at a young age. Despite prior candidate gene studies, the genetic cause of canine renal dysplasia remains unclear. It is unknown if the same gene is affected in all breeds with renal dysplasia or if different genetic variants exist in each breed.

We recently conducted a preliminary genome-wide association study in boxers with renal dysplasia. The analysis suggests an association adjacent to a gene previously implicated in human hypodysplasia, a common cause of pediatric kidney disease. In this grant we propose genetic and functional studies to identify the causative mutation in boxers. We also propose to collect additional samples from Boxers and other breeds affected by renal dysplasia (including miniature schnauzers, soft coated wheaten terriers and Shetland sheepdogs) to allow genome-wide association analysis of additional cases of renal dysplasia in boxers and other breeds to be performed in the future. This will help us dissect the genetics of canine renal dysplasia, improve our understanding of renal development in dogs and humans, and determine whether breed specific genetic tests will be required for prevention.

So far this year we have performed targeted large-scale sequencing of the candidate disease region linked to juvenile renal dysplasia in boxer. We have found a large number of differences between sick and healthy dogs and continue to carefully analyzing these to determine which variant might be the causative mutation. The primary candidate gene is an excellent candidate, making us enthusiastic about the further study of this gene.

Sample collection from other breeds is ongoing and we welcome the help from pet owners and breed clubs in collection samples. We are emphasizing miniature schnauzers, soft-coated wheaten terriers and Shetland sheepdogs, but are interested in working with any breed. Information and consent forms can be found at: http://www.broadinstitute.org/dogsamples.