

**2016 NATIONAL GENERAL MEMBERSHIP
HEALTH RESEARCH REPORT
Ginger Jones – Health Research Coordinator**

CHF RESEARCH GRANTS:

STATUS REPORTS FOR GRANTS WE SUPPORT:

Research grant #1753 *Identification of genetic modifiers that impact clinical expression of arrhythmogenic right ventricular cardiomyopathy in the Boxer dog – Dr. Kate Meurs*

Description: Arrhythmogenic right ventricular cardiomyopathy is a genetic-based heart disease in adult dogs that was recently found to be due to a deletion mutation in the striatin gene. Dogs with this genetic mutation can suffer from irregular heartbeat, loss of consciousness and sudden death. Dr. Meurs' lab has demonstrated that Boxer dogs with 2 copies of a genetic deletion (homozygous) are most likely to have the more severe form of the disease, however dogs with 1 copy of the mutation are more likely to have variable disease; some will become quite sick while others will remain free of clinical signs. The mechanism for the variability in clinical signs is unknown but is thought to be associated with the concurrent inheritance of other genetic factors. Dr. Meurs' research will determine if additional genetic factors exist, thus greatly improving our ability to use and interpret the genetic test for the striatin mutation.

While this study was conducted only on the Boxer breed, because of the penetrance in this breed, much is learned about the genes associated with severe cases of this disease. The knowledge of the gene areas associated with this disease, or candidate genes, allows a more narrowed focus for research on other dog breeds and provides both a significant savings in time and costs associated with similar research. Attached is the research status report to date. There is a request to extend at no cost the continuance of the research project for valid reasons cited, so there will be another final research report forthcoming..

NEW GRANTS WE WILL BE SUPPORTING FOR 2016:

From the list of new grants received from Samantha Wright, grants coordinator for CHF, we have selected the following 3 grants to support financially.

02242: Understanding the Genetics of Adverse Drug Reactions in Sighthounds Principal Investigator: Dr. Michael H. Court, PhD; Washington State University Total Grant Amount: \$150,000.00; Grant Period: 2/1/2016 - 1/31/2018

Project Abstract: Life-threatening unanticipated reactions to drugs with a narrow margin of safety (such as those used for anesthesia and to treat cancer) are a common concern for dog owners and veterinarians. However, research conducted at Washington State University has enabled development of a simple cheek swab test (the MDR1 gene test) that is now being used by veterinarians to identify dogs that should either avoid or have reduced doses of certain drugs used to treat cancer and parasite infections. Using a similar strategy the investigators have been conducting research to identify the cause of extremely slow recovery from anesthesia (up to several days) in a high proportion of greyhounds, and also in other sighthound breed dogs (such as Scottish deerhound, Borzoi, Whippets, etc.). The investigators have recently discovered a mutation in a gene that is known to be essential for metabolism (breaking down) many commonly used anesthetic drugs (such as propofol), as well as many other drugs

used in dogs. Interestingly in addition to sighthound breeds, this gene mutation is also found in some other breeds such as Border Collies. The purpose of this research project is to prove that this mutation can cause decreased drug metabolism, while also determining which drugs and which dog breeds are likely to be most impacted. The ultimate goal of this study is to develop a genetic test that could be used by veterinarians to guide the safe use of these drugs in dogs with the gene mutation

02233-A: Evaluation of a Novel Technique for Gastric Decompression in Dogs with Gastric Dilatation and Volvulus

Grant Status: Open

Grant Amount: \$12,960

Dr. J. Brad Case, DVM, MS, University of Florida

November 1, 2015 - April 30, 2017

Breed(s): -All Dogs

Research Program Area: Gastrointestinal Disease

Abstract

Gastric dilatation-volvulus (GDV) is a common medical and surgical emergency that involves severe gas distention and malposition of the stomach in dogs. GDV results in profound distension of the stomach which compresses vital blood vessels and organs within the abdomen, thus reducing oxygen delivery to these organs. The ultimate result is tissue death and toxins in the blood stream. Surgery is necessary to correct the condition, and overall mortality rates range from 10-50% depending on severity and duration of gastric dilatation. For this reason, rapid and effective decompression of the stomach is critical for successful treatment of dogs with GDV. Currently, approaches to decompression have a temporary effect and gas can re-inflate the stomach within minutes. Oftentimes affected dogs are not near a facility with surgical capabilities when they develop signs of GDV. Owners may then need to drive hours to a facility in which emergency stabilization and surgery can be performed. In this study, a new, minimally-invasive technique, similar to that used in human medicine, will be tested for its ability to immediately and continuously alleviate the gas distention in the stomach of GDV patients using a specialized catheter, thus allowing the patient to be stabilized and/or transported for surgery. This relatively inexpensive and rapid procedure could have far-reaching impact for dogs with this devastating condition.

02215: A Cancer Vaccine for Canine Osteosarcoma

Grant Status: Open

Grant Amount: \$80,974

Dr. Rowan J Milner, BVSc, University of Florida

January 1, 2016 - December 31, 2017

Sponsor(s): American Boxer Charitable Foundation

Breed(s): -All Dogs

ABSTRACT

Osteosarcoma is a malignant cancer that carries a very poor prognosis in most large breeds of dogs. The standard of care treatment for osteosarcoma is surgery followed by chemotherapy. Unfortunately, a large number of these osteosarcomas undergo early metastasis (spread) even with early surgical intervention and chemotherapy. Infections of the surgery site, especially when limb-sparing surgery is used, have been known to stimulate the immune system post-operatively in dogs, resulting in improved survival. Since overall survival is bleak in patients with osteosarcoma, developing an osteosarcoma cancer vaccine holds promise as an adjunct treatment to surgery and chemotherapy. In a previous study of 400 dogs with melanoma we showed that a vaccine containing the ganglioside (GD3) causes a

measurable immune response in normal dogs and dogs with melanoma, and prolonged survival. In this study, 40 dogs with osteosarcoma presenting to the University of Florida Small Animal Hospital will be randomly assigned to two treatment groups. Twenty dogs will be vaccinated using a ganglioside-based cancer vaccine following standard of care treatment. The outcome of the dogs receiving the vaccine plus standard of care will be compared to 20 dogs who receive standard of care without vaccination. Vaccines will be administered monthly for 4 treatments and the dogs monitored every 3-6 months for life or until lost to follow-up. The outcome of this study will help us understand the immune process associated with cancer vaccines for osteosarcoma and with an ultimate goal to improve survival for dogs with this aggressive form of cancer.

HEART RESEARCH FUNDRAISING PROJECT:

Special thanks and recognition goes to Renee McCartin and her support group for their continued efforts and dedication to fundraising for heart research via the calendar project. So far this year BCOA Health has received about \$2600 from the calendar sales to support our CHF heart research grants.

Date: 12/31/2015

AKC Canine Health Foundation Progress Report CHF Grant Number 01753

Project Title Identification of genetic modifiers that impact clinical expression of arrhythmogenic right ventricular cardiomyopathy in the Boxer dog

Institution North Carolina State University

Principal Investigator: Kathryn Meurs

Project Start Date: 1/1/2013

Report Number 5

It is the policy of AKC Canine Health Foundation not to disclose information from progress reports of sponsored studies to any individual, club, organization, CHF grant committee member, peer reviewer or company if the information contains data that, in the opinion of the CHF or the investigator, represents a conflict of interest.

The CHF sponsors research studies and contractually requires all investigators to provide periodic progress reports. The Foundation makes grant payments based on satisfactory progress of the study. Research progress is evaluated based on reviewing information provided by the researcher including the initial schedule of work to be performed and progress reports. These reports relate to the research methodology without drawing conclusions regarding research results. The CHF shares the non-confidential section of progress reports with donors who contribute to CHF a significant percentage of the cost of the study. This sharing by CHF is intended to nurture the interest of the donor in both the sponsored study and canine health research in general. Sponsors may also be in a position to assist the research in the identification of any additional dogs for the study. The policy is also designed to assure the donor that his/her money is being well spent and the CHF is closely monitoring the study.

Study Objectives

Objective 1: Identify 100, 7 year old boxer dogs that are positive heterozygous for the striatin mutation, 50 with less than 100 VPCs/24 hours (low disease expression) and 50 with at least 500 VPCs/ 24 hours (high disease expression)

We have evaluated 136 dogs. Eight-four met the criteria for the study. Fifty-nine meet the criteria for high disease expression, 25 meet the criteria for low disease expression.

Objective 2: Perform genome wide association on the 100 samples collected above to identify an association between genes located on specific chromosomal regions and the level of expression of disease.

DNA samples were collected on all dogs. We have performed the genome wide association. Strong regions of statistical significance were located on Chromosomes 9 and 16. We evaluated the strongest region of interest on chromosome 9 with targeted gene sequencing as well as the region on chromosome 16 and other possible candidate regions in 5 dogs with severe disease and 5 with mild disease. We looked for DNA variants that were significantly different between the two groups. Variants that are consistently different are evaluated with Sanger sequencing of a larger number of animals in the laboratory. We have not yet identified anything that is statistically significantly different between the two groups. However, we have identified variations in 10 cardiac genes that are found in dogs with severe disease and not with mild disease. One is a splice site variant in the Nerve Growth Factor gene which influences sympathetic innervation and would be expected to influence cardiac arrhythmias. One is a 5 base pair deletion in an atrial natriuretic protein (ANP) gene that we have observed in the more severe dogs. The ANP gene has been shown in some humans to have polymorphisms that could be modifiers of cardiomyopathy. We are also looking at a stop codon formation in the ATP6V0E2 gene (see attached figure). This is a gene involved in hydrolyzing ATP for energy in the cell which could also be involved with arrhythmia development. At this point we have about \$ 3,000 left in the fund and are requesting a final short no cost extension to finish the Sanger Sequencing of these remaining gene alterations in a larger number of dogs with severe disease and not mild.

Non-Confidential , Lay language Progress Summary

At this point we have been able to identify that that are genetic differences between dogs with the mild form of ARVC and dogs with the severe form even though all of them have one copy of the striatin deletion. However, we are not yet sure if these genetic differences actually cause the difference in disease severity or a simply factors of these dogs coming from different lines and families. We have now narrowed the differences down to DNA variations in 10 genes that have important heart implications and that are found only in the dogs with the severe disease but not the mild disease. At this point we need to do some additional work to determine if these are always found in severe dogs when we look at a larger number of dogs, and not in the mild dogs. We are doing this now with the samples we have already collected and hope to have it completed very shortly.

Publications:

None so far

No Cost Extension Request:

We have requested a no cost extension to complete the final Sanger Sequencing part of this project. The samples are already collected and we can do the work ourselves rather than sending it to a large sequencing core so we do not anticipate further delays!