GRANT PROGRESS REPORT REVIEW

Grant: 00762: *The Mapping and Characterization of Canine Epilepsy Loci*

Principal Investigator: Dr. Gary S. Johnson, DVM PhD

Research Institution: University of Missouri, Columbia

Grant Amount: $129,600.00

Start Date: 10/1/2008 **End Date:** 9/30/2010

Progress Report: 24 month

Report Due: 9/30/2010 **Report Received:** 1/31/2011

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: Epilepsy is a neurological condition characterized by seizures which result from abnormal brain activity. There is no cure and the medications used to reduce the frequency of seizures are often ineffective and/or have unsatisfactory side effects. While there is strong evidence that canine epilepsy is inherited in many breeds, the patterns of inheritance are often complex.

Objective: The researchers' goal is to identify mutations responsible for epilepsy so that they can devise DNA tests that detect the mutations. These tests can be used by dog breeders to help them avoid matings that produce puppies destined to develop epilepsy. The researchers have collected DNA samples from over 1100 epileptic dogs and nearly 6000 of their relatives. The researchers will study epilepsy in dog breeds from their collection. Then, they will use DNA samples from these four breeds and appropriate mapping strategies to determine the locations of the epilepsy mutations on the dog chromosomes. Then they will examine the genes at these chromosomal locations to identify epilepsy-causing mutations. DNA tests that detect these mutations will be validated and then offered to the dog-owning public.

Grant Objectives:

Objective 1: To verify and update the medical histories of the members of the targeted canine epilepsy families and to expand the pedigrees by obtaining DNA samples and medical histories from additional family members.

Objective 2: To use SNPchip technology and case/control allele association analysis to map the epilepsy loci in as many dog breeds as possible.

Objective 3: To use homozygosity testing and other fine mapping techniques to narrow the target regions in the mapped epilepsy loci and to identify the mutations responsible epilepsy by resequencing candidate genes found within the narrowed chromosomal regions.

Objective 4: To devise DNA tests for suspect epilepsy mutations and to determine if the results of these tests consistently predict the correct phenotype in the mapped breed and in the other breeds.

Publications:

Report to Grant Sponsor from Investigator:
The projects investigators collected DNA from nearly 10,000 epileptic dogs and their close relatives and they have assembled epilepsy?family pedigrees in 28 different dog breeds. The investigators have re?contacted the owners of over 2,000 dogs in this collection to obtain additional clinical information or to confirm that the "normal" dogs have remained seizure free. They have used samples from 13 different breeds in 15 different experimental attempts to identify the chromosomal locations of epilepsy?causing genetic mutations. They used an experimental procedure known as a genome?wide association study (GWAS) which is done with a device known as a SNPchip. SNPchips compare the DNAs from epileptic dogs to the DNAs from non?epileptic family members at tens or hundreds sites in all of the chromosomes. Eight of the GWASs were done in collaborations with other laboratories and seven were done at the University of Missouri. Thirteen of the GWASs were applied to epilepsies in which seizures were the only symptoms. None of these studies provided strong evidence about the chromosomal locations of epilepsy?causing mutation; however, some of them provided weak evidence, suggesting possible chromosomal sites for epilepsy mutations. The investigators examined genes at five of these sites, but failed to find any epilepsy?causing mutations. By contrast, both GWAS for diseases with symptoms in addition to seizures successfully identified the chromosomal locations of the responsible locations. The GWASs for the pure epilepsies probably failed because causes of epilepsy in some of the family members were different from the causes in other family members and/or because the epilepsies resulted from a complex combination of genes and acquired factors.