RESEARCH PROGRESS REPORT SUMMARY

Grant 02257: Identification of Genetic Risk Factors for Canine Epilepsy

Principal Investigator: Gary Johnson, DVM, PhD

Research Institution: University of Missouri, Columbia

Grant Amount: $110,081.00

Start Date: 5/1/2016 **End Date:** 7/30/2018

Progress Report: Mid-Year 2

Report Due: 4/30/2018 **Report Received:** 5/22/18

(The content of this report is not confidential and may be used in communications with your organization.)

Original Project Description:

Epilepsy is one of the most common neurologic diseases of dogs and a top concern of dog breeders. Despite strong evidence that genetics is important in determining the risk of idiopathic epilepsy, numerous gene mapping studies have failed to identify a locus that accounts for that risk in either dogs or humans. Seizures occur when excessive activity goes beyond the normal threshold for brain function, many factors contribute to that level of activity, and therefore, mutations in numerous genes may collectively contribute to increased activity until that threshold is exceeded, resulting in epilepsy. Any one of these mutations may be present in non-epileptic dogs, but because it only partially alters activity, it would not produce seizures. Therefore, traditional gene mapping studies might overlook that mutation. Using a novel whole genome sequencing approach the investigators hope to identify DNA variations in epileptic dogs that could affect the function of genes such as ion channels and neurotransmitter receptors that have been shown to alter the seizure threshold in humans or rodents. The frequency of such variations in populations of epileptic and non-epileptic dogs will be directly compared rather than the indirect markers used in traditional mapping studies. The increased power provided by looking for specific gene candidate variations rather than linked markers will aid the identification of epilepsy risk factors, perhaps leading to development of DNA tests to enable breeders to select against such risk factors.

Publications:

Kolicheski, A., Barnes Heller, H. L., Arnold, S., Schnabel, R. D., Taylor, J. F., Knox, C. A., . . . Katz, M. L. (2017). Homozygous PPT1 Splice Donor Mutation in a Cane Corso Dog With Neuronal Ceroid Lipofuscinosis. J Vet Intern Med, 31(1), 149-157. doi:10.1111/jvim.14632

Kolicheski, A., Johnson, G. S., Villani, N. A., O'Brien, D. P., Mhlanga-Mutangadura, T., Wenger, D. A., . . . Katz, M. L. (2017). GM2 Gangliosidosis in Shiba Inu Dogs with an In-Frame Deletion in HEXB. J Vet Intern Med, 31(5), 1520-1526. doi:10.1111/jvim.14794

Presentations:

Searching for Genetic Risk Factors for Canine Epilepsy in Whole Genome Sequences. Presented by GS Johnson at the National Parent Club Canine Health Conference in St Louis on 8/12/17.

Report to Grant Sponsor from Investigator:

This study has two parts. Part 1 is to first use the DNA from epileptic purebred dogs to produce whole genome sequences and to identify potential breed-specific genetic risk factors that increase the likelihood that a dog will develop epilepsy. We proposed to generate and analyze whole genome sequences from at least 18 epileptic dogs. So far whole genome sequences from 23 epileptic purebred dogs have been generated and analyzed. Samples from five additional epileptic dogs have very recently been sequenced at a sequencing center in St. Louis, Missouri and we expect to complete the initial analysis of the sequence data from these five dogs in the next two or three weeks. The second step to part 1 is to select high-priority breed-specific genetic factors and use DNA tests to see if they occur more often in epileptic dogs then in non-epileptic dogs of the same breed. We proposed to evaluate at least seven high-priority breed-specific genetic factors. So far we have completed the evaluation of six of them, but none have proven to be genetic risk factors for epilepsy. Preliminary results for a seventh genetic risk factor, this one in English Setters, look promising; however, we will need to complete testing and statistical analysis to validate our findings. Work is just started on an eighth potential breed-specific genetic factor. In addition, we expect to evaluate additional risk factor candidates identified in the last five whole genome sequences.

The second part of the study is to analyze our entire collection of whole genome sequences from both epileptic and non-epileptic dogs to identify and genetic factors that increase the risk for developing epilepsy in multiple breeds. As soon as the final five whole genome sequences from part one become available, we will add them our database of whole genome sequences and begin work on part 2. Initially we proposed to evaluate 15-to-25 candidate risk factors. We expect new alternative technology to enable the evaluation of twice that many epilepsy risk factor candidates.