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: $112,781
Start Date: 5/1/2016 End Date: 12/31/2018
Progress Report: FINAL
Report Due: 12/31/2018 Report Received: 2/28/2019

(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.

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.
Publications:

Report to Grant Sponsor from Investigator:

This investigation of canine epilepsy had two objectives: (1) to identify genetic variation that occurs within a single breed and increases the chances for breed members to develop epilepsy; and (2) to identify genetic variation that occurs in many breeds and increases the chances of developing epilepsy for any dog that carries the variation. For objective 1, we first determined entire genome sequences for 28 epileptic dogs from 19 different breeds. Computer analysis was used to determine which of the millions of DNA sequence variations in each of these genome sequences, were likely to alter the functions of genes previously associated with epilepsy in human patients or animal models. We selected eight of the variants considered most likely to be epilepsy risk factors and did DNA tests to see if the variants were more common in epileptic dogs than in non-epileptic dogs from the same breed. For four of these variants, the DNA test results suggested that they were not epilepsy risk factors. DNA test results for the other four variants suggested that they may be breed-specific epilepsy risk factors; however, one of them was too rare to be useful even within the affected breed. Another of these variants appears to slightly increase epilepsy risk but is too common to be of practical use. Breeding strategies that avoid this risk factor would eliminate much of the breed’s gene pool. The remaining two potential epilepsy risk factors show promise and are the subjects of ongoing investigation.

For the second objective (identification of genetic risk factors for epilepsy that occur in multiple breeds), we did a computer screen for potential epilepsy risk factors in over 150 genome sequences, mostly from dogs with diseases other than epilepsy. We then selected the 55 variants considered most likely to be epilepsy risk factors and tested for the concentrations of these variants in pooled DNA samples from 604 epileptic dogs representing 33 different breeds. The concentrations of these variants were also measured in pools of DNA from 604 breed and gender matched non-epileptic dogs that reached at least their eighth birthday without a history of seizures. The concentrations of 3 of the variants were significantly higher in the epilepsy pools compared to the control pools. These three potential epilepsy risk factors should be validated with other collections of DNA samples from epileptic and non-epileptic dogs before used to for mate selection.