RESEARCH PROGRESS REPORT SUMMARY

Grant 02172-MOU: Understanding Hereditary Deafness in Dogs

Principal Investigator: George Strain, PhD

Research Institution: Louisiana State University

Grant Amount: $120,015.00

Start Date: 11/1/2015 **End Date:** 4/30/2018

Progress Report: End-Year 2

Report Due: 10/31/2017 **Report Received:** 10/27/2017

This report includes progress reporting from English Setter samples as well as Dalmatians and Australian Cattle Dogs. The English Setter samples are funded under a separate CHF grant #2387-MOU with the English Setter Association of America.

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

Original Project Description:

Hereditary deafness associated with white pigmentation occurs in numerous dog breeds. The breeds most affected are the Dalmatian (Dal, 22% unilaterally deaf, 8% bilaterally deaf) and the Australian cattle dog (ACD, 11.4% and 3%). The mechanism of inheritance is unknown, and previous studies to determine the mode of inheritance and locate the causative gene(s) have thus far been unsuccessful.

Using a modified twin study approach, full-sibling littermates will be clinically and genetically evaluated. Like human twins, full siblings should have very similar DNA, which will reduce the variability of their DNA when compared to studies of unrelated dogs. Using the Illumina CanineHD Beadchip, which contains 172,115 DNA markers (SNPs) spread uniformly across the canine chromosomes, markers will be compared between the sibling pairs, and differences between siblings at individual markers will thus be identified. Using this approach candidate deafness genes can be identified and will advance the current understanding of this heritable disorder.

Funding for the research is provided through the efforts and generosity of the Australian Cattle Dog Health, Education, and Welfare, Australian Cattle Dog Club of America, Dalmatian Club of America, and the Dalmatian Club of America Foundation. The AKC Canine Health Foundation supports this effort and will oversee administration of funds and scientific progress reports.

Publications:

None at this time.

Report to Grant Sponsor from Investigator:

We exceeded our goal of samples collected (50 pairs of each breed), reaching 114 ACDs, 127 Dals, as well as 64 English setters. Samples which have been run through Illumina beadchip reads are 183 Dals, 101 ACDs, and 33 ES. Several additional samples await analysis and we anticipate receipt of a few additional promised samples. Samples were collected in litter mate pairs where one dog hears and one is deaf in one or both ears, with the assumption that the DNA from litter mates is more similar than that of unrelated dogs, thereby reducing data variability and increasing the likelihood of identifying a causative gene. Similar past studies of unrelated dogs failed to identify a causative deafness gene. Limited samples have been collected from other breeds with pigment-associated hereditary deafness for later comparison when a causative gene is identified. DNA analyses have been performed on most ACD and Dal samples using Illumina CanineHD Beadchip arrays (containing 172,115 SNPs (markers) spread uniformly across the canine genome) to identify SNPs that significantly differ between affected and unaffected siblings.

Thirty-five deafness-associated SNPs were found from all three breeds, but there was little overlap in SNPs between the breeds. The statistical significance for many associated SNPs was not high enough to be considered meaningful by conservative measures. Probabilities (P-values) approaching our threshold of 10-6 were found for SNPs on one chromosome in ACDs, two chromosomes in Dals, and two chromosomes for combined DAL/ACD/ES data. We cannot yet with certainty say that the same gene defect is responsible for deafness in all three breeds.

Public gene databases and research publications on genes associated with human deafness as well as genes associated with auditory structure and function have been screened to build a catalog of genes associated with deafness or auditory function or pigmentation, and whose location is close to the SNPs identified in the breeds. Over 4,000 were identified by those methods, but have been winnowed down to less than 200 at present. These identified genes will next be evaluated for sequencing in DNA from hearing and deaf ACDs and Dals. If the number of genes to be sequenced is determined to be excessive, whole genomes will instead be sequenced for both hearing and deaf dogs of both breeds. Potential collaborative agreements with other research groups are being explored to expand the number of subjects included in the bioinformatics analyses as well as possible funding sources to cover the costs of analyzing a large number of additional samples.