GRANT PROGRESS REPORT REVIEW

Grant: 00963: *Genotyping Small Breed Dogs with Portosystemic Vascular Anomalies and Microvascular Dysplasia*

Principal Investigator: Dr. Sharon A. Center, DVM

Research Institution: Cornell University

Grant Amount: $189,489.00

Start Date: 6/1/2008 **End Date:** 11/30/2010

Progress Report: 24 month

Report Due: 5/31/2010 **Report Received:** 7/3/2010

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: Portosystemic vascular anomalies (PSVA) and microvascular dysplasia (MVD) are related genetic disorders causing malformation of the liver circulation. This trait affects a number of small pure breed dogs, causing high serum bile acid values (SBA) and has a prevalence ranging from 30% to 80% in various breeds and related dogs.

Objective: The goal is to identify a genetic marker for PSVA/MVD that will allow development of a genetic test. Extensive pedigree studies support an autosomal dominant but incompletely penetrant mode of transmission, explaining the dismal success of attempted trait elimination based on SBA. It is important to eliminate this trait because affected dogs cause owner dissatisfaction, financial burden, and negative breed publicity, in addition to patient suffering. The researchers have discovered significant linkage between the PSVA/MVD trait and genetic markers on one chromosome in a large family of Tibetan Spaniels. Findings have been confirmed with flanking markers and demonstration of similar linkage in Cairn Terriers, Maltese, and Havanese. The researchers will pursue further genetic mapping (microsatellites, SNPs) of the PSVA/MVD trait in these and additional breeds, and undertake association mapping using DNA banked from unrelated pure breed dogs with PSVA (n=70). Candidate genes associated with abnormal vascular development in humans will be explored.

Grant Objectives:
Objective 1: Test informative 3 generation pedigrees of Havanese, Shih Tzu, Yorkshire Terriers, Miniature Schnauzers, Pugs, Norwich Terriers, and Norfolk Terriers segregating a clinically identical PSVA/MVD trait with microsatellite markers encompassing the region identified as linked in Tibetan Spaniels, Cairn Terriers, and Maltese.

Objective 2: Undertake SNP genotyping, within the region of interest surrounding the peak LOD score location, in each dog breed with confirmed linkage.

Objective 3: After narrowing the minimal LD interval to a few hundred kilobases or less by SNP haplotyping, we will sequence candidate regions.

Objective 4: Develop a disease-risk test that may be used to screen dogs for the PSVA/MVD trait, even if a specific mutation is not identified.

Publications:

Report to Grant Sponsor from Investigator:
Collateral information from our Genome-wide SNP mapping study in Cairn Terriers, crossover analysis of MSS2 markers in Cairn Terriers (a separate study), and development of our Canine Fetal Liver Transcriptome (a separate study) have identified regions to interrogate, consistent with a complex trait- multiple gene hit hypothesis. We are using this additional information to provided additional SNPs in the fine mapping region and to prioritize candidate genes. With the fine mapping SNP data, supplementary SNP information in hand, our Fetal Liver Transcriptome database, and recognition of an emerging loci haplotype, we have identified important candidate genes near each locus associating with the PSVA/MVD trait.

Several strategies may assist further refinement of loci involved with the PSVA/MVD trait and identification of the mutations. Upon discovery of putative mutations, we will investigate their consistency within related affected and non-affected dogs in our pedigrees and in normal controls. According to our multiple gene hit hypothesis, we expect all affected dogs to have at least one copy of the mutation at loci of interest whereas unaffected dogs will lack one or more loci mutations.