



AMERICAN KENNEL CLUB  
**CANINE HEALTH  
FOUNDATION**  
PREVENT TREAT & CURE

## 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:** 12/31/2011 (no cost extension approved)

**Progress Report:** 36 month

**Report Due:** 5/31/2011      **Report Received:** 6/8/2011

**Recommended for Approval:** Approved

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*(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:**

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.

The goal is to identify genetic markers for PSVA/MVD that will allow development of a genetic test. This research grant focuses on the fine-mapping within genomic regions of interest (ROI) found to be associated with PSVA/MVD from genome-wide association studies, and it focuses on candidate gene sequencing across several breeds and in a component of a larger cooperative research program. Extensive pedigree studies and genetic screening using several technologies (microsatellites, SNPs, transcription expression, haplotype analysis) have shown and continues to support the original theory that PSVA/MVD is a polygenic and complex trait.

There has been a delay in fine-mapping of the genome regions in order to most efficiently utilize the grant funds. New technologies allowed the researchers to build their genome-wide association data and refine the region of interest (ROI). The researchers are now using evolving new technology to finish the fine mapping in all associated regions.

Several candidate genes have been investigated. The exons in the genes have been sequenced but a mutation that could alter protein structure or expression has not been found. The un-translated regions in the genes are continued to be analyzed using new sequencing technologies. The researchers also continue to pursue new candidate genes as they are identified.