GRANT PROGRESS REPORT REVIEW

Grant: 01151: Molecular Basis of Tricuspid Valve Dysplasia
Principal Investigator: Dr. Paula S. Henthorn, PhD
Research Institution: University of Pennsylvania
Grant Amount: $98,929.80
Start Date: 1/1/2009   End Date: 6/30/2012

Progress Report: 36 month
Report Due: 12/30/2011   Report Received: 12/30/2011

Recommended for Approval:

(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: Tricuspid valve dysplasia (TVD) in dogs involves defects of the tricuspid valve, which result in changing degrees of blood leakage between the chambers of the right side of the heart. Dogs with the most severe malformations usually develop right-sided congestive heart failure within the first few years of life. Many dogs are only mildly affected at birth, and are not identified until after they have become breeding animals. Labrador Retrievers, in particular, seem to be predisposed to TVD. A previous study determined that TVD in one large pedigree of Labrador Retrievers was inherited as an autosomal dominant trait. Genetic analysis of these dogs mapped a susceptibility gene to canine chromosome 9, but the inheritance of this susceptibility gene was not simple, which agrees with an independent study on a larger population of dogs that did not reveal a simple mode of inheritance.

Objective: The researchers are continuing to examine Labrador Retrievers through clinical cardiology examinations, pedigree analysis, and DNA analysis, with the goal of identifying a mutant allele of a gene or genes responsible for TVD. Once found, genetic testing procedures can be developed to identify dogs at risk for developing clinical signs and for passing the disease to their offspring.

Grant Objectives:
Objective 1: To perform dense SNP genotyping in the region of the previously mapped TVD on the dogs of the original large pedigree, using the canine whole genome SNP chip (Affymetrix) in
order to narrow the disease locus interval. Informative SNP markers will be used to screen additional dogs to find the minimal conserved haplotype associated with TVD, thus narrowing the previously mapped CFA9 TVD susceptibility locus.

Objective 2: To collect DNA from dogs (mostly Labrador Retrievers) that have been examined by echocardiography, including both TVD affected and unaffected dogs. From this material, we will:

a. Evaluate the presence of the previously mapped TVD locus on CFA9 in this wider sampling of affected and suspicious Labrador Retriever dogs, with the goals of narrowing DNA interval on CFA9 that contains the TVD susceptibility, and

b. Examine the patterns of inheritance of TVD in additional Labrador Retriever pedigrees with the goals of identifying appropriate samples for additional studies that could identify other genetic factors contributing TVD and explain the complex mode of inheritance.

Objective 3: Sequence candidate genes to identify the disease-causing allele of the CFA9 locus, providing the basis for DNA-based genetic testing that can be used to control the incidence of TVD in Labrador Retrievers, and potentially in other breeds.

Publications:

Report to Grant Sponsor from Investigator:
Tricuspid valve dysplasia (TVD) is a developmental anomaly of the tricuspid valve of the heart, seen in many dog breeds, that has clear evidence of a genetic predisposition in the Labrador Retriever. While inheritance patterns in this breed are not simple, the disease showed autosomal dominant inheritance with incomplete penetrance, in a previous mapping study in one pedigree of Labradors. In this study, a 4Mb region on dog chromosome 9 was associated with the occurrence of this disorder. The purpose of our study was to expand the study of this region, with the immediate goal of refining our knowledge of the location of the "TVD gene". We identified additional useful polymorphic markers spanning the previously identified 4 Mb disease-associated interval for analysis on the original pedigree, and on a collection of TVD affected dogs and their relatives, and performed SNP chip hybridization and analysis on 41 dogs. Our studies in this larger population of Labrador Retrievers, not as closely related, did not identify the chromosome 9 region as associated with TVD. Consequently, we will need to continue collecting DNA from additional TVD affected dogs and their relatives to perform a large genome wide association study. As before these studies would be aimed at the development of linked marker and mutation-based tests that can be used by breeders to reduce the incidence of this heart defect in the breed. Tricuspid valve dysplasia (TVD) has been documented in numerous dog breeds, including Boxers, German Shepherds, Golden Retrievers, Great Danes, Great Pyrenees, Irish Setters, Mastiffs, Newfoundland, Old English Sheepdogs, Shih Tzu, and Weimaraners, and may have a genetic basis in some of these breeds. We expect to generate knowledge and reagents with which to examine TVD affected dogs of other breeds to determine if their disease is related to that found in Labrador Retrievers.

A successful outcome from this research could improve the overall quality of life of dogs of many breeds, and further the knowledge of congenital heart disease in veterinary medicine. It may also inform human pediatric medicine, since Ebstein anomaly in children is the comparable disease in humans.