



GRANT PROGRESS REPORT

Grant: 00919: *Molecular Genetic Characterization of Canine Cystinuria for the Development of Carrier Tests*

Principal Investigator: Dr. Paula S. Henthorn, PhD

Research Institution: University of Pennsylvania - School of Veterinary Medicine

Grant Amount: \$48,924.00

Start Date: 7/1/2008 **End Date:** 12/31/2009

Progress Report: 12 month

Report Due: 6/30/2009

Report Received: 6/24/2009

Recommended for Approval: Approved

Original Project Description:

Cystinuria is an inherited disorder that causes kidney and urinary tract stones in dog, man and other animals and has been documented in over 60 breeds of dogs. In humans, mutations in two genes (named SLC3A1 and SLC7A9) are found in affected individuals. While human cystinuria was originally observed to be inherited as an autosomal recessive trait, more complex inheritance patterns, and their molecular origins, are currently being elucidated. Based on our previous work, which developed tests to detect cystinuria-causing mutations for Newfoundlands and Labrador Retrievers, breeds that have autosomal recessive forms of the disease, and for Australian Cattle Dogs, which have a more complex etiology for cystinuria. We will focus our efforts for the next funding period on experiments that test a hypothesis developed from our current work. In particular, we will concentrate on three breeds in which cystinuria is more common, in order to understand the genetic basis of the most common form of cystinuria in dogs, with the goal of developing carrier tests to be used for the elimination of cystinuria in multiple breeds.

Original Grant Objectives:

Objective 1: Continue to determine the relationships between excess urine cystine, clinical signs/manifestations of cystinuria, age, and gender, particularly in breeds where cystinuria is more common.

Objective 2: Analyze polymorphisms in and flanking the SLC3A1 and SLC7A9 genes.

Objective 3: Perform linkage/association studies for markers on the X-chromosome in Mastiffs, Scottish Deerhounds, Irish Terriers, Cardigan Welsh Corgis, and English Bulldogs.

Objective 4: perform additional studies in regions of the X chromosome that are implicated, or
b) recruit additional DNA and urine samples necessary to perform a whole-genome association study in the future.

Publications:

6-30-09 Two publications are in preparation at this time, one to report the mutations in Labrador retrievers and Australian Cattle dogs, and a second to report the clinical and biochemical features of cystinuria in the breeds with later onset of stone formation.

Report to Grant Sponsor from Investigator: (Lay Update allowed to be reproduced)

Cystinuria is an inherited disorder that causes kidney and urinary tract stones in dog, man and other animals and has been documented in over 60 breeds of dogs. In humans, mutations in two genes (named SLC3A1 and SLC7A9) are found in affected individuals. In humans, cystinuria is primarily inherited as an autosomal recessive trait, with some instances of more complex inheritance patterns. In many dog breeds, cystinuria appears much more complex. Our data rules out recessive inheritance of mutations changing the proteins produced by SLC3A1 or SLC7A9. It also suggests that, in some breeds at least, the sex of the dog and environmental factors may affect the expression of cystinuria. We are pursuing these issues and employing whole genome analysis, using canine SNP ("snip") chips, in our ongoing studies.