AMERICAN KENNEL CLUB
CANINE HEALTH FOUNDATION

GRANT PROGRESS REPORT

Grant: 00927: *Gene Discovery in Hereditary Cerebellar Abiotrophy of Scottish Terriers*

Principal Investigator: Dr. Natasha Olby, VetMB PhD

Research Institution: North Carolina State University

Grant Amount: $54,810.00

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

Progress Report: 18 month

Report Due: 6/30/2009 **Report Received:** 6/19/2009

Recommended for Approval: Approved

Original Project Description:
A hereditary neurodegenerative disease called a cerebellar abiotrophy has emerged as a significant problem in the Scottish Terrier. The disease causes neuronal death in the cerebellum, resulting in progressive loss of coordination. Signs appear between three and 24 months of age and progress until the animal is incapacitated; currently there is no treatment. The disease is inherited in an autosomal recessive manner therefore carriers of the disease are normal. As a result, the abnormal gene has been spread within the Scottish Terrier breeding population. We have collected DNA samples from affected dogs and their relatives and we will genotype families of these affected dogs using a set of markers that span the canine genome at regular intervals. Linkage analysis will be performed with the data to link a chromosomal region to the disease. Candidate genes in the linked regions will be sequenced to identify mutations. In the absence of candidate genes, linked regions will be saturated with closely spaced markers to narrow the region of interest, facilitating sequencing of genes in the area.Once the abnormal gene has been identified, a genetic test will be developed to identify carriers andaffected dogs.

Original Grant Objectives:
Objective 1: Phenotype confirmation and DNA/RNA banking from families of affected Scottish terriers

Objective 2: Identification of chromosomal region(s) linked to cerebellar abiotrophy in Scottish terriers
Objective 3: Identification of candidate genes in linked chromosomal regions

Objective 4: Sequencing of candidate genes to identify the causative mutation

Publications:
As of 6-30-09: A paper titled: "Hereditary Cerebellar Degeneration in Scottish Terriers: Clinical and Histopathological Findings" has been prepared for submission to the Journal of Veterinary Internal Medicine and is just undergoing a final review by all authors prior to submission.

As of 6-30-09: A paper describing the detailed histopathology is in preparation for submission to Veterinary Pathology.

Report to Grant Sponsor from Investigator: (Lay Update allowed to be reproduced)
In this project we aimed to better define the phenotype of Scottish Terriers with Cerebellar Degeneration, to bank DNA from as many affected and related normal dogs as possible and to perform a genome-wide screen to look for linkage of trait to a specific chromosomal region. If a linked region was identified, candidate genes in the region were to be investigated further.

We have continued to collect and bank DNA samples from Scottish Terriers and now have DNA from 45 affected dogs and 115 normal dogs. During the course of the last 18 months, many Scottish Terrier owners and breeders have helped us in this endeavor and we are grateful for their support. We have obtained histopathological confirmation of the diagnosis in an increasing number of dogs, we presented this data at the American College of Veterinary Internal Medicine Annual Forum in June 2008 and have prepared a scientific paper describing the disease in detail. As a result of the presentation, neurologists are more aware of this disease in Scottish Terriers and know to contact us if they see an affected dog.

We have performed a genome-wide screen with microsatellites, followed by linkage analysis that has revealed one possible region of interest with a LOD score >2 that we are investigating further by additional genotyping. Concurrent to this, we also performed a genome wide screen with SNPs in 72 dogs at a neurogenetics laboratory at NIH, followed by an association study. This did not reveal any significant association to the disease but has a lower sensitivity than the linkage study. Over the next 3 months we will continue to map the region with the promising LOD score using additional markers and additional families of dogs where possible to determine whether this is a statistically significant finding. If it is, we will fine map the region using SNPs to focus down to possible candidate genes. Progress is good, Dr Urkasemsin, the PhD student working on this project has worked extremely hard to generate and analyze all the data so far. We are of course disappointed that we don't have a significant LOD score to work with yet, but are encouraged that there is one region that still holds promise.

Thank you for the ongoing support you have shown us – we hope that we will ultimately identify the underlying mutation and develop a test for the disease.

Natasha Olby