



GRANT PROGRESS REPORT REVIEW

Grant: 00925: *Identification of Mutations Causing Hereditary Cerebellar Cortical Degeneration in American Staffordshire Terriers and Old English Sheepdogs*

Principal Investigator: Dr. Natasha Olby, VetMB PhD

Research Institution: North Carolina State University

Grant Amount: \$64,800.00

Start Date: 4/1/2008 **End Date:** 3/31/2010

Progress Report: 18 month

Report Due: 9/30/2009

Report Received: 9/14/2009

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.)

Original Project Description:

Background: American Staffordshire Terriers and Old English Sheepdogs suffer from similar, but likely distinct, hereditary neurodegenerative diseases of the cerebellum. In both breeds the disease is inherited in a recessive fashion and the underlying mutation has become widely dispersed in the population. The researchers have collected DNA from affected dogs and their relatives in both breeds and have genotyped them using markers spaced at regular intervals throughout the genome. They have used the resulting data to link a chromosomal region to the disease trait. The researchers have established linkage in both breeds of dog; the disease is linked to a different chromosomal region in each breed.

Objective: In this project the researchers will identify candidate genes for the disease in linked regions using published information on the canine genome. These genes will be sequenced to identify mutations. If there are no good candidate genes, they will saturate the linked regions with closely spaced markers, thus narrowing the target region to the extent that all genes contained within can be sequenced. Identifying the mutation in either of these breeds will be relevant for additional breeds of dog that have similar diseases such as the Scottish Terrier and Gordon Setter.

Original Grant Objectives:

Objective 1: Identify candidate genes in linked chromosomal regions

Objective 2: Perform high-density mapping of linked chromosomal regions

Objective 3: Sequence candidate genes

Publications:

- Olby NJ, Harris T, Mehta PM, Breen M, Thomas R, Myers R, Nielsen D. Linkage analysis in American Staffordshire Terriers with hereditary cerebellar cortical degeneration. *J Vet Intern Med* 2008;22:723-724

- Olby NJ, Mehta PM, Flegel T, Blot S, Abtibol M. Clinical and neuropathological findings in American Staffordshire terriers with cerebellar cortical degeneration. *Proc ACVIM*, Montreal June 2009.

- Abitbol M, Thibaud J-L, Olby N, Hitte C, Puech J-P, Hédan B, Dréano S, Brahimi S, Uriarte A, Delattre D, Bernex F, André C, Gray F, Delisle F, Caillaud C, Panthier J-J, Aubin-Houzelstein G, Blot S, Tiret L. Sulfatase Deficiency Associated with Neuronal Ceroid Lipofuscinosis. Submitted to *Science*, September 2009.

Report to Grant Sponsor from Investigator:

Report for American Staffordshire Terrier

During this project, the genomic association for Cerebellar Cortical Degeneration in American Staffordshire Terriers was identified through microsatellite analysis. In the genomic region of interest, candidate genes were identified. The first two genes sequenced did not result in a mutation. We identified a third gene however, prior to sequencing this gene, a group in France that we have been collaborating with told us they thought they had found the mutation. In our discussions, we found they had sequenced that same gene (the name of which I can't disclose until the publication comes out). The DNA samples from the US dogs were used to confirm the mutation. A genetic test has been developed by the group in France led by Dr Abitbol, and is being offered by Antagene in France and Optigen in the US.

Report for Old English Sheepdog

We have continued to make progress on this grant. We have collected DNA from more extended families and in the last 3 months we have finished genotyping all chromosomes to ensure that there were no other regions of interest (in our initial work we stopped our screening once we got the positive LOD score on chromosome 4 because of concerns over the quantity of DNA available). We did find one additional chromosome with a LOD score of 2. This will be evaluated further. We also discovered an error in assignment of IDs for the dogs used in the SNP analysis through family analysis and comparison of gender (established from the SNP data). The error was generated by the equipment assigning IDs as if we had used a human SNP chip (this was the first run of the canine Illumina SNP chip). Once the correct IDs had been assigned, we found a region of homozygosity in affected dogs in the region with the positive LOD score. We are therefore continuing our efforts to sequence genes in this region.