GRANT PROGRESS REPORT REVIEW

Grant: 00748: *SNP Association Mapping for Canine Epilepsy*

Principal Investigator: Dr. Ned Patterson, DVM PhD

Research Institution: University of Minnesota

Grant Amount: $235,872.00

Start Date: 4/1/2007 **End Date:** 9/30/2010

Progress Report: 30 month

Report Due: 9/30/2009 **Report Received:** 9/30/2009

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: Epilepsy is a serious, often inherited, seizure disorder affecting a large number of breeds. The inconsistency in seizure types between breeds suggests that many different genes are likely to contribute to canine epilepsy.

Objective: This project aims to identify chromosomal regions associated with epilepsy in English Springer Spaniels and Australian Shepherds, as a start to identify the contributing gene or genes, and to develop a marker test. The researchers expect to identify an associated chromosome region or regions in English Springer Spaniels and Australian Shepherds, and to develop a screening genetic marker test. Future studies could then look in other breeds to see if they share the same genetic risk factor(s). If successful, this project would serve as excellent proof of the usefulness of this technology for epilepsy and lead to full - scale testing of other breeds in future studies.

Original Grant Objectives:
Objective 1: To collect more samples from epileptic and control English Springer Spaniels and Australian Shepherds, and dogs from other breeds.

Objective 2: To map IE within English Springer Spaniels and Australian Shepherd by whole genome association using a SNP array.

Objective 3: To develop a diagnostic screening marker linkage test with marker haplotype(s) in the ESS or AS IE locus or loci that are in linkage disequilibrium with the trait and determine positional candidate genes within the loci.

Publications:

Report to Grant Sponsor from Investigator:

English Springer Spaniels:

We now have over 900 samples from English Springer Spaniels with over 90 dogs with recurrent seizures. In the past year we have done extensive seizure surveys, phone interviews, and rechecking all dogs status to be sure dogs included in SNP analysis have the correct diagnosis. Our previous pedigree and segregation analysis indicated that idiopathic epilepsy in this breed was most likely not a simple Mendelian (one gene fully penetrant) trait and that the pedigrees available were of marginal power to detect a genetic locus, so we did not attempt a genetic linkage analysis. Rather, we concentrated on selecting a sample set that is most appropriate for a genetic association study with single nucleotide polymorphism (SNP) markers. To date, we now have run 59 affected and 101 unaffected ESS for genome wide marker analysis, which is an additional 24 affected dogs and 67 unaffected dogs since our last progress report 6 months ago. We continue to have weak association and on 3-4 chromosomes with one that is slightly stronger, but further studies with more dogs are still needed since none of the hits reach statistical significance.. We plan to analyze as many additional dogs for which we can get DNA and accurate medical information for in the next 6-12 months, and also our goal is to also re-analyze all ESS on the new Illumina 150,000 -200,000 SNP array which have just become available and is much more powerful than the previous arrays.

It has become increasingly apparent that IE is likely to be polygenic in many breeds. Our, formal agreement with the U of MO and Finland allows us to compare possible chromosomal areas across breeds - ESS and Aussie's (also Vizlsas and other breeds) in case there is a shared gene across breeds in which putting the data together might be more efficient in identifying the specific gene. Dr. Patterson attended the LUPA meeting in May 2009 in Sweden and met in person with Dr. Hannes Lohi about all of the Epilepsy projects with an emphasis on the data in ESS,(and Aussies, and Vizslas). In Dr. Lohi's upcoming presentation to the American Epilepsy Society in December 2009 in Boston regarding more than 15 breeds it is clear that are a limited number of breeds where one gene may cause epilepsy, but it in many breeds the genetic predisposition is influenced by more that one gene which is very likely to be the case for ESS. Despite the complexity in ESS, we are committed to continue following through on our search for markers and genes in ESS as long as funds are available.

Australian Shepherds:

For Australian Shepherds there are over 150 affected Aussies and over 1100 total samples banked between us and our collaborators of the University of Missouri-Columbia. We are continuing to try to collect more Aussie DNA samples to be sent to our lab for this and any needed future analysis, and to verify the diagnosis whenever possible.

With our formal written agreement for the sharing of Australian Shepherd samples and data between the U of MO, Hannes Lohi in Finland, and us, we are attempting to not unnecessarily repeat DNA testing to ensure maximum efficiency and the best use of funds. 38 cases and 39 controls from US Aussies collected by Dr. Johnson's lab have been analyzed in Europe by Dr.

Lohi. The results do not reveal any single association peaks, indicating that the epilepsy is either caused by more than one gene or there might be different type of epilepsies present in Aussies.

The best association was found on one specific chromosome, but this did not reach statistical significance with this number of dogs analyzed. There were 3other chromosomes too with weak association and further studies with more dogs are required to confirm the initial results. In the last six months we have collected 15 additional affected Aussie's and 15 additional controls and the University of Minnesota, and our goal is to have 47 more affected, and 46 more controls Aussies total.. Dr. Lohi and we have held off additional SNP analysis for Aussies in the last 6 months waiting for the new 150,000 - 200,00 Illumina SNP array which has just become available and has much more power that the previous Illumina (and Affymetrix) SNP arrays). Our goal is to analyze 85 affected 85 unaffected Aussies on the new arrays in the next 6-12 months including re-analyzing all of the original 38/39 Aussies. Drs Patterson and Lohi meet in Sweden in May of 2009 with an emphasis on the data in Aussies, ESS (and Vizslas). In Dr. Lohi's upcoming presentation to the American Epilepsy Society in December 2009 in Boston regarding more than 15 breeds it is clear that are a limited number of breed where one gene may cause epilepsy, but it in many breeds the genetic predisposition in influenced by more that one gene which is very likely to be the case for Australian Shepherds. Despite the complexity, we are committed to continue following through on our search for markers and genes in Australian Shepherds as long as funds are available.