RESEARCH PROGRESS REPORT SUMMARY

Grant 02488: Addison's Disease and Symmetrical Lupoid Onychodystrophy in Bearded Collies Provide Common Ground for Identifying Susceptibility Loci Underlying Canine Autoimmune Disorders

Principal Investigator: Anita Oberbauer, PhD

Research Institution: University of California, Davis

Grant Amount: $118,458.00

Start Date: 5/1/2018 **End Date:** 4/30/2020

Progress Report: End-Year 1

Report Due: 4/30/2019 **Report Received:** 4/23/2019

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Original Project Description:

Hypoadrenocorticism or Addison's disease (AD) is a life-threatening condition that afflicts multiple dog breeds and results from autoimmune destruction of the adrenal glands. Similarly, another canine autoimmune condition that causes pain and suffering is Symmetrical Lupoid Onychodystrophy (SLO). Both AD and SLO are postulated to be complexly inherited and preliminary data suggest a common set of susceptibility genes working in concert with additional genes that determine expression of either disease. For the study of AD and SLO the investigators will focus on the Bearded Collie breed due to its relatively high prevalence of both conditions and a genomic structure favorable for identifying variations in the DNA. The investigators will scan the entire canine genome using genetic markers coupled with whole genome sequencing to identify chromosomal regions that harbor genetic changes contributing to disease manifestation. The disease risk conferred by each of these genetic variants, or quantitative trait loci (QTL), will then be calculated to develop a tool for selecting sires and dams early in life, thereby allowing breeders to choose mating pairs that will produce offspring with a low likelihood of developing AD and SLO.

Publications:

Gershony, L. C., Belanger, J. M., Short, A. D., Le, M., Hytönen, M. K., Lohi, H., … Oberbauer, A. M. (2019). DLA class II risk haplotypes for autoimmune diseases in the Bearded Collie offer insight to autoimmunity signatures across dog breeds. *Canine Genetics and Epidemiology*, *6*(1), 2. https://doi.org/10.1186/s40575-019-0070-7

The second manuscript, addressing the results from GWAS, is under preparation.

Presentations:

Upcoming poster and short talk:
Gershony, L.C.; Belanger, J.M.; Hytönen, M.K.; Lohi, H.; Oberbauer, A.M. "Novel locus associated with Symmetrical Lupoid Onychodystrophy identified in Bearded Collies carrying particular DLA class II risk haplotypes". 10th International Conference on Canine and Feline Genetics and Genomics. Bern, Switzerland. May 26-29, 2019.

Report to Grant Sponsor from Investigator:

Hypoadrenocorticism or Addison's disease (AD) is a life-threatening condition that afflicts multiple dog breeds and results from autoimmune destruction of the adrenal glands. Similarly, another canine autoimmune condition that causes pain and suffering is Symmetrical Lupoid Onychodystrophy (SLO). Both AD and SLO are postulated to be complexly inherited, where disease expression depends on a combination of genetic and environmental factors. Identification of the genetic components involved in disease susceptibility may help understand and predict risk for disease.

Our preliminary data in Bearded Collies suggested a common set of susceptibility genes for AD and SLO working in concert with additional genes that determine expression of either disease. For the study of AD and SLO we targeted the Bearded Collie breed due to prevalence of both conditions and a genomic structure favorable for identifying variations in the DNA. We have obtained all the SLO, AD and control Bearded Collie samples proposed in the grant for the genotyping and genome-wide association (GWA) analyses. For SLO, there was a genome-wide significant peak on CFA 12, a region approximately 8Mb long and harboring the DLA class II genes. We have determined an association between the DLA class II genes and SLO risk (Gershony, Belanger et al. 2019). When we undertook a second GWA analysis that included only dogs that carried at least one of the DLA class II risk haplotypes for SLO, a second genome-wide significant peak appeared spanning a 6 Mb region of CFA 17. The region contains 18 RNA genes and 14 protein-coding genes, including three potential candidate genes for SLO disease expression. Association between the same genes but different DLA class II haplotypes and AD was also identified in our study (Gershony, Belanger et al. 2019). For AD, we are in the process of analyzing the GWAS data accounting for the DLA class II association. These findings will be presented at the International Conference on Canine and Feline Genetics and Genomics 2019.

Our next step is to use the regions of association for each disease identified by the GWAS to guide analysis of whole genome sequencing (WGS) to identify actual mutations that contribute to disease manifestation. Samples from 21 Bearded Collies (6 AD, 6 SLO and 9 controls) have been submitted for WGS and the data are expected to be in the lab by June 2019. The remaining 2 AD and 3 control samples needed to meet the numbers stated in the grant are actively being recruited with assistance of

the breed club. We will be using the WGS data already obtained for identification of genetic mutations associated with each disease as soon as the WGS samples currently being sequenced become available. The initial association of the DLA with each disease has been published. We are in the process of preparing a publication on the second genetic association identified in the GWAS for SLO.