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

Start Date: 5/1/2018 **End Date:** 12/31/2020

Progress Report: End-Year 2

Report Due: 4/30/2020 **Report Received:** 3/3/2020

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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. (2019). “Genetic Characterization of Two Autoimmune Diseases that Afflict Bearded Collies: Symmetrical Lupoid Onychodystrophy and Primary Hypoadrenocorticism (Addison’s disease)” (Unpublished doctoral dissertation). University of California, Davis.

Gershony, L. C., J. M. Belanger, A. D. Short, M. Le, M. K. Hytönen, H. Lohi, T. R. Famula, L. J. Kennedy and A. M. Oberbauer (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

Gershony LC, Belanger JM, Hytönen MK, Lohi H, Oberbauer AM (2019). "Novel Locus Associated with Symmetrical Lupoid Onychodystrophy in the Bearded Collie." Genes 10(9):635. https://doi.org/10.3390/genes10090635

Presentations:

Poster presentation 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) consists of a life-threatening clinical condition that afflicts multiple purebred and mixed breed dogs. The condition results from autoimmune destruction of the adrenal glands leading to life-long cortisol deficiency. Similarly, another autoimmune condition causing pain and suffering to dogs is Symmetrical Lupoid Onychodystrophy (SLO). For the study of AD and SLO we are investigating the Bearded Collie breed due to the relatively high prevalence of both conditions in this breed and a genomic structure favorable for identifying DNA variations. All SLO, AD and control Bearded Collie samples proposed in the grant for genotyping and genome-wide association (GWA) analyses have been collected and processed. After removing closely related individuals from the dataset, GWA analysis for SLO revealed genome-wide significant peaks on CFAs 12 and 17; the region of association on CFA12 harbors the DLA class II genes for which we have already determined an association (Gershony et al. 2019). The region on CFA 17 was more strongly associated with phenotype when only dogs that carried DLA class II risk haplotypes for SLO were considered. Promising candidate genes were identified in both regions of association, and WGS data for SLO and healthy controls is currently under analysis for identification of potential causative mutations. A similar approach was used for AD. Initial GWAS done on 103 unrelated dogs (41 cases, 62 controls) showed a single genome-wide significant peak; additional data analysis revealed two other regions of association on two different chromosomes all of which contain potential candidate genes involved in immune function and regulation. Dogs carrying multiple risk genotypes across these regions are at greater risk of AD. Two manuscripts have now been published as a result of this study and a third manuscript will be submitted for publication by the end of March. Samples from 21 Bearded Collies (6 AD, 6 SLO and 9 controls) have been submitted for WGS and variant data obtained. Analysis of whole genome sequencing (WGS) is underway to identify mutations that contribute to disease development in these dogs. Regions of association identified in GWAS will be prioritized, followed by exploration of the entire genome. Four new DNA samples (2 AD and 2 controls) have been collected and will be

submitted for WGS next week. The remaining control sample needed to meet the numbers stated in the grant is actively being recruited with assistance of the Bearded Collie Foundation for Health (BeaCon) and regional US Bearded Collie breed clubs. We deeply appreciate the continued assistance of BeaCon, Bearded Collie breed clubs and owners in our studies.