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

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Progress Report: FINAL

Report Due: 12/31/2020 **Report Received:** 12/18/2020

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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., Belanger, J. M., Hytönen, M. K., Lohi, H., & Oberbauer, A. M. (2019). Novel Locus Associated with Symmetrical Lupoid Onychodystrophy in the Bearded Collie. *Genes*, *10*(9), 635. https://doi.org/10.3390/genes10090635

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

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. Working with breeders and owners, all proposed numbers of SLO, AD and control Bearded Collie samples were obtained, genotyped, and analyzed in genome-wide associations (GWAs). GWA analysis for SLO revealed significant peaks on canine chromosomes (CFA) 12 and 17; the region of association on CFA12 also harbors the DLA class II genes for which we have already determined an association (Gershony et al. 2019). The region on CFA17 was more strongly associated with the SLO phenotype when only dogs that carried DLA class II risk haplotypes for SLO were considered. Promising candidate genes were identified 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. The GWAS showed a single genome-wide significant peak on CFA18 whose association was not further enhanced when the DLA class II genes were included. Three other regions of suggestive association were noted on different chromosomes and found to contribute risk to AD development. Within the Bearded Collies we studied, dogs without the risk variants at the four loci were at reduced risk for AD whereas dogs carrying multiple risk genotypes across these regions were at increased risk of AD. Potential candidate genes involved in immune function and regulation were identified within the regions identified as associated with AD risk. To characterize the actual variants responsible for SLO and AD risk, 27 Bearded Collies (9 AD, 7 SLO and 11 controls) have been whole genome sequenced (WGS) and the variant data is being analyzed within the regions of association identified in the GWAS, which will be followed by exploration of the entire genome. Three manuscripts have now been published as a result of this study. We deeply appreciate the continued assistance of BeaCon, Bearded Collie breed clubs and owners in our studies.