OAK GRANT Progress Report

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 higher 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. Genetic studies often benefit from studying dogs that are not closely related; that is, based upon pedigree information, dogs related up to the grandparent level should be avoided. However, another thing to consider is that dogs that appear unrelated based on their pedigree information could still be genetically similar if they descend from the same ancestor a few generations prior. Therefore, to ensure that the findings were not limited to only a single line of dogs, the genetic relatedness was calculated based on their genotype information and dogs that were too similar were removed from the GWA study. The GWA analysis for SLO revealed genome-wide significant peaks on CFAs (canine chromosomes) 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.

A similar approach was used for AD. Initial GWA analysis done on 103 unrelated dogs (41 cases, 62 controls) showed a single genome-wide significant peak; additional data analysis revealed three other regions of association on three different chromosomes all of which contain potential candidate genes involved in immune function and regulation. Dogs carrying multiple risk genotypes across these four regions are at greater risk for AD. Two manuscripts have now been published as a result of this study, and a third manuscript focusing on the results of our AD GWA analysis was recently submitted for publication and is in the process of peer review.

All of the blood samples needed for the whole genome sequencing (WGS) portion of the study have been collected and processed, and WGS data from AD, SLO and healthy controls are currently under analysis for identification of potential causative mutations contributing to disease development in the Bearded Collie. Regions of association identified in each GWA study will be prioritized for both diseases (AD and SLO), followed by exploration of the entire genome. We deeply appreciate the continued assistance from the BeaCon Foundation, Bearded Collie breed clubs and owners in our studies.

Published manuscripts:

Gershony LC, Belanger JM, Hytönen MK, Lohi H, Oberbauer AM. Novel Locus Associated with Symmetrical Lupoid Onychodystrophy in the Bearded Collie. Genes (Basel). 2019 Aug 22;10(9):635. doi: 10.3390/genes10090635.

Gershony LC, Belanger JM, Short AD, Le M, Hytönen MK, Lohi H, Famula TR, Kennedy LJ, Oberbauer AM. DLA class II risk haplotypes for autoimmune diseases in the bearded collie offer insight to autoimmunity signatures across dog breeds. Canine Genet Epidemiol. 2019 Feb 15; 6:2. doi: 10.1186/s40575-019-0070-7.