RESEARCH PROGRESS REPORT SUMMARY

Grant 02709: Identification of Genetic Risk Factors Contributing to Gastrointestinal Motility Disorders

Principal Investigator:	Leigh Anne Clark, PhD
Research Institution:	Clemson University
Grant Amount:	$57,930.00
Start Date: 2/1/2020	**End Date:** 7/31/2022
Progress Report:	FINAL
Report Due: 7/31/2022	**Report Received:** 10/26/2022

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Original Project Description:

Gastrointestinal motility disorders affect the nerves and muscles of the esophagus, stomach, and/or the intestines, causing digestive disturbances. Congenital idiopathic megaesophagus (CIM) is an esophageal motility disorder of dogs wherein contractility is reduced and leads to an enlargement of the esophagus. Affected puppies regurgitate after eating and survivors are susceptible to life-threatening complications. The highest incidences of CIM occur in the Great Dane and German Shepherd Dog breeds. Gastric dilatation-volvulus (GDV or bloat) is characterized by dilatation and twisting of the stomach, cutting off blood and oxygen to the organs. Based on a previous study for CIM in Great Danes, the investigators will 1) study a narrow region of chromosome 6, shown to be a major risk factor for CIM; 2) seek additional genomic regions that contribute to CIM, and 3) determine association between CIM and GDV based on shared genetic risk factors that impact gastrointestinal motility. The investigators hope to establish a pattern of transmission and develop a genetic test to reduce the incidence of CIM, and potentially GDV, in Great Danes.

Publications:

Sarah M. Bell, Jacquelyn M. Evans, Katy M. Evans, Kate L. Tsai, Rooksana E. Noorai, Thomas R. Famula, Dolores M. Holle, Leigh Anne Clark.. Congenital idiopathic megaesophagus in the German shepherd dog is a sex-differentiated trait and is associated with an intronic variable number tandem repeat in Melanin-Concentrating Hormone Receptor 2. PloS Genetics, 2022 (in press)

*Sarah (Murphy) Bell was supported on 02709 while completing the above study. She was also funded by a CHF fellowship for the GSD work.

Bell SM, Evans JM, Evans KM, Tsai KL, Noorai RE, Famula TR, Holle DM, Clark LA (2022) Congenital idiopathic megaesophagus in the German shepherd dog is a sex-differentiated trait and is associated with an intronic variable number tandem repeat in Melanin-Concentrating Hormone Receptor 2. PLoS Genetics18(3): e1010044. (Cover Feature)

Bell SM, Friedenberg S, Tsai K, Evans JM, Clark LA (2022) Genetic investigation of congenital idiopathic megaesophagus in Great Danes. (in preparation)

Presentations:

Evans JM, Congenital idiopathic megaesophagus is associated with a variable number tandem repeat in Melanin-Concentrating Hormone Receptor 2 in German shepherd dogs. Oral presentation ICCFGG in Huntsville, AL October 2022

Report to Grant Sponsor from Investigator:

We have obtained DNAs from 122 Great Danes: 69 having congenital idiopathic megaesophagus (CIM), and 54 that are unaffected; among these are 5 Great Danes that have survived a gastric dilatation-volvulus (GDV) event and 23 healthy Great Danes that are at least 5 years old, have no history of clinical signs of esophageal or gastric dilatation, and have not undergone prophylactic gastropexy. We successfully employed a modern technique where we generated partial, low cost genome-wide genetic sequence profiles for 83 Great Danes (45 cases, 38 controls) and then created a custom reference panel from 624 dogs and an analysis pipeline to fill in missing data for each dog. Using over 2 million variants from the across the genome, we validated our methods by accurately mapping previously identified causal loci for multiple coat colors of the Great Dane. We then carried out a genome-wide association study (GWAS) for CIM in which we identified a single, novel region that is significantly associated with the disease. None of the variants in the associated region lie within the coding portion of a gene and current efforts are aimed at determining which, if any, of these variants are important for gene regulation. CIM-risk alleles were detected in Great Danes having gastric dilatation-volvulus (GDV), but our study size was insufficient to determine if an association exists. We also generated whole genome resequencing data for 4 unrelated Great Danes that will be used to increase imputation accuracy in future studies and to probe sequences in the CIM-associated region for candidate causal variants.