RESEARCH PROGRESS REPORT SUMMARY

Grant 02297-MOU: Understanding the Genetics of Hepatic Copper Toxicosis in the Dalmatian

Principal Investigator: Andrew Mason, PhD

Research Institution: University of Alberta

Grant Amount: $107,668

Start Date: 3/1/2017 **End Date:** 8/31/2022

Progress Report: End-Year 5

Report Due: 2/28/2022 **Report Received:** 2/28/2022

(The content of this report is not confidential and may be used in communications with your organization.)

Original Project Description:

Copper toxicosis, leading to early death from liver disease, was first described in Bedlington Terriers in 1975, with similar diseases described in other dog breeds including the Labrador Retriever, West Highland White Terrier, Skye Terrier, and Doberman Pinscher. Genes have been linked to copper toxicosis in the Bedlington Terrier and the Labrador Retriever, but the genes differ by breed. In most breeds the genes are not known. Copper toxicosis was considered rare in the Dalmatian but may be more common than previously believed. Symptomatic dogs may be misdiagnosed as having other liver diseases, never appropriately diagnosed or only diagnosed with copper overload at a terminal stage. The investigators aim to identify the faulty gene(s) in Dalmatians using an advanced whole genome sequencing strategy to obtain the genome sequences of carefully selected members of an affected Dalmatian pedigree. Identification of the problem gene is the first step towards genetic testing and to improved breeding practices necessary to eradicate hepatic copper toxicosis from the Dalmatian breed. Gene identification will help raise awareness of copper toxicosis in the Dalmatian breed, lead to more rapid diagnosis of the condition, and support the search for the most effective therapy.

Funding for the research is provided through the efforts and generosity of the Dalmatian Club of America and Dalmatian Club of America Foundation. The AKC Canine Health Foundation supports the funding of this effort and will oversee grant administration and scientific progress.

Publications: None at this time.

Presentations:

09.01.19

Twedt DC. Hepatic Copper Storage Disorder in the Dalmatian. Dalmatian Club of America, Betty Garvin Memorial Speaker Series, Colorado Springs, USA. May 9, 2018 (ORAL).

Macintyre G, Stothard P, Twedt D and Mason AL. Understanding the Genetics of Hepatic Copper Toxicosis in the Dalmatian. GI Research Day, Division of Gastroenterology, Medicine, Faculty of Medicine & Dentistry, U Alberta, Edmonton, Canada. May 1st, 2018 (POSTER) https://sites.google.com/ualberta.ca/gi-reserach-day-2018/home

Macintyre G (Stothard P, Twedt D and Mason AL). Genetic culprits in canine copper hepatopathies. March 11th, 2020. Medical Genetics, Faculty of Medicine & Dentistry, University of Alberta.

Macintyre G (Stothard P, Twedt D and Mason AL). Hepatic copper toxicosis in the Dalmatian: analyses of known canine CT-associated genes. Annual City-wide GI Research Day. Tuesday, April 28, 2020. Hosted by the Division of Gastroenterology, Medicine, Faculty of Medicine & Dentistry, U Alberta, Edmonton, Canada. CANCELLED.

Report to Grant Sponsor from Investigator:

Dalmatians may be at risk of inheriting a rare copper storage disorder of the liver, canine copper toxicosis (CT). CT can be fatal and can quickly spread through a pedigree if left unmanaged. The disorder is known to affect several breeds, including the Bedlington Terrier and Labrador. The problem genes have been identified in these two breeds. Many dogs respond to copper chelation therapies. Early identification of dogs-at-risk either prior to the appearance of symptoms, or at an early stage of copper accumulation, can save lives. A genetic test can help to identify dogs-at-risk in early life. The test can also help to reduce the spread of problem genes by enabling breeders to make informed choices prior to breeding carriers of CT-associated genes.

We are working with the DCA Copper Storage Disorder Study Group (CSDSG) to try to understand the extent of the problem in Dalmatians in the US and Canada. Our studies indicate that CT in the Dalmatian is likely an inherited condition, as in other breeds. We are now in the process of tracking some genetic variants across our pedigree to find the culprit gene, or genes. We hope to understand the root cause of the disorder, to develop a genetic test to improve the lives of affected dogs, and to help eradicate CT from the Dalmatian breed.

Objective 1 (to better understand CT prevalence) and objective 2 (to identify candidate genes) are almost complete, and the third aim, to develop a CT gene test to enable rapid testing, is underway.

We would like to thank the CSDSG, DCA and AKC Canine Health Foundation for the opportunity to evaluate CT in the Dalmatian breed, and all of the concerned breeders who have committed funds and information in support of these studies. The recruitment phase for the study is now complete, and we

will no longer accept samples directly for the study. However, you can still join the study and provide information on your dog and its relatives. For further information, please contact our study coordinator, Dr Georgina Macintyre, at gm3@ualberta.ca.

ACKNOWLEDGEMENTS
As always, we really do appreciate the efforts of Mrs Ann Ball and her colleagues in the CSDSG, Mrs Cindee Gootee and Mrs Tracie Tepke who continue to reach out to the Dalmatian community in support of CT research.
We would also like to thank the CSDSG, DCA and AKCCHF for the opportunity to evaluate CT in the Dalmatian breed, and all concerned breeders who have committed funds and information in support of these studies.
We do appreciate your continued patience and the approval of yet another extension on this project.