



RESEARCH PROGRESS REPORT SUMMARY

Grant 03113: Investigation of Candidate Genetic Variants for Copper-associated Hepatopathy in the Dalmatian

Principal Investigator: Andrew Mason, PhD

Research Institution: University of Alberta

Grant Amount: \$79,396.85

Start Date: 2/1/2023 **End Date:** 7/31/2024

Progress Report: End-Year 1

Report Due: 1/31/2024 **Report Received:** 2/2/2024

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Original Project Description:

Canine copper-associated hepatopathies (CAHs) are now being diagnosed at increasing frequency across North America. The Dalmatian breed is no exception with cases being regularly reported in recent decades. The balance between genetics and the environment is unclear. Increased levels of copper in commercial diets may exacerbate a fragile genetic predisposition. Other studies around the world suggest that even in breeds with an obvious genetic component, that strong genetic modifiers might reduce the impact of a strong disease-associated variant. Investigators' previous AKCCHF-funded study indicates a very strong genetic component to CAH in the Dalmatian, with several lines affected and a shortlist of candidate genetic variants that require further investigation to support their credibility. The research team has observed some family-specific changes associated with copper processes and further work is needed to understand their significance by interrogating the regions around some candidate variants that do not reside in genes. In the next phase of the study, long-read sequencing may help us to link isolated variants to genes, and fill in sequence gaps for some dogs. This powerful technique enables continuous reads for a great distance along DNA, and will confirm and extend our findings, and bring us closer to an explaining CAH in the Dalmatian. Lifelong copper chelation and dietary modifications can provide relief, but early diagnoses and treatment are essential to avoid fatality. As in all breeds, CAH in the Dalmatian is complex and well-understood genetic test(s) will be a major step towards the eradication of liver copper disorders from the Dalmatian breed.

Publications:



August 2023: plan to write and submit a manuscript on the inheritance patterns of CAH in the Dalmatian, and the status of the known canine CAH-associated genes in the breed (we will submit a draft to CHF when available).

Presentations:

None at this time.

Report to Grant Sponsor from Investigator:

In the Dalmatian, our studies suggest that canine hepatic copper storage disorder (HCSD), an excessive accumulation of copper in the liver (sometimes >10,000ppm liver copper) is very likely due to a primary genetic defect in a copper pathway gene, or genes, and can lead to liver failure, if not recognized. This condition needs to be caught early to ensure successful intervention via copper chelation. Canine copper-associated hepatopathies are usually milder, associated with intermediate levels of copper accumulation, and are a complex group of liver disorders that include a liver copper accumulation that may result from a genetic predisposition and/or an environmental component, such as high levels of bioavailable copper in some commercial diets.

In the Dalmatian, our studies indicate that inheritance of HCSD is autosomal recessive in nature, potentially similar to copper storage disorders in humans (Wilson Disease) and other dog breeds. Using the most effective sequencing strategies available, we continue to search for a culprit gene in these lines that may explain the disorder and lead to a genetic test.

However, our analyses of recent study recruits have revealed a complexity to copper accumulation in the Dalmatian, and in some of our lines, we cannot rule out the potential influence of multiple genes, dietary copper, or inflammation, on liver function, and the term Copper-Associated Hepatopathy (CAH) may be more applicable to some study recruits. Understanding this complexity in canine copper storage disorders is important to identifying the appropriate Dalmatians for genetic studies.

We are recruiting new dogs to our study. We remain interested in litters with no known liver health issues, and those that include HCSD-affected Dalmatians, with a confirmed diagnosis of excessive copper accumulation in the liver. We would like to remind all Dalmatian breeders to take the opportunity to also submit blood samples for DNA extraction to the OFA DNA repository (<https://ofa.org/about/dna-repository/>) for use by all researchers funded through CHF. Your participation may support our goal of finding the gene(s) that contribute to CAH and HCSD in the Dalmatian. We appreciate the efforts of all breeders and owners who have responded to our requests to date. For more information on our study, please contact Dr Georgina Macintyre (gm3@ualberta.ca, Dr Andrew Mason's group, University of Alberta, Edmonton).