



RESEARCH PROGRESS REPORT SUMMARY

Grant 02157-MOU: Genomics of Deafness in the Dalmatian

Principal Investigator: Claire Wade, PhD

Research Institution: University of Sydney

Grant Amount: \$120,960.00

Start Date: 1/1/2015 **End Date:** 12/31/2018

Progress Report: FINAL

Report Due: 12/31/2018 **Report Received:** 12/13/2018

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

Original Project Description:

Congenital deafness is a health issue that has higher prevalence in certain breeds, including the Dalmatian. Other studies in this breed have found the trait to be inherited in a complex rather than simple Mendelian manner. Using a large number of samples from animals that have been tested for hearing status, Dr. Wade will employ the latest genomic technologies and computational analyses to conduct this study. The ultimate goal is to identify mutations underlying the trait of congenital deafness in the Dalmatian breed and work towards a genetic testing solution for the Dalmatian breeding community.

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

Publications:

Thesis: Ms Jennifer Liu (attached to a prior report)

Presentations:

Honors student Lucy Armstrong has presented the results of her analysis at internal student forums.



We presented a poster on the project at the International conference on Canine and Feline genomics in Minnesota USA in July 2017.

Simone Carter: Honors presentation "Association of external phenotype with deafness risk loci in the Dalmatian" - this presentation was an outline of the work to be conducted for her honors research project.

Thesis: Ms Jennifer Liu (attached to a prior report)

Verbal presentation: Ms Simone Carter to honours student peer group on plans for the study to associate external phenotype with genotype.

Sample sheet for judging critique (attached).

Scheduled presentation at the World Small Animal Veterinary Association meeting in Canada 2019

Report to Grant Sponsor from Investigator:

Aims

1. That we can identify mutations underlying the risk signals identified by previous analysis of genotyped samples
2. That we can validate already identified loci in a wider cohort of samples and detect loci that confer greater relative-risk of disease
3. That we can ascertain gene frequencies for risk loci within the Dalmatian breed
4. That we can provide genetic tests for one or more risk loci

Our team carried out mutation detection and validation testing in six different chromosomal regions to identify any that appeared to impact the occurrence of deafness in a wider sample of the breed. The six regions were originally identified by observing regions that segregated in near perfect concordance with phenotype when comparing four bilateral deaf and two bilateral hearing Dalmatians by next generation sequencing (Illumina HiSeq). As a part of the funded project we undertook to conduct whole genome analysis of a further 130 dogs. Because we were uncertain of the mode of inheritance and the relationship between bilateral deafness and unilateral deafness on a genetic level, we tested five different statistical models on the regions. The array analysis continued to support most of the regions that we had chosen to study. The continued support of the regions suggests that deafness in the breed is likely not a simple Mendelian trait. Our work provided validation support for the earlier risk haplotype that had been identified earlier in Dalmatians and weaker support for a locus reported to impact a similar phenotype in the Australian Stumpy-Tailed cattle dog.

We cannot yet provide a test for a functional mutation in the region but have identified a haplotype on chromosome 20 that statistically impacts the occurrence of bilateral deafness in the breed. It is possible that the trait of unilateral deafness may be impacted by other loci. The risk locus on chromosome 20 is not completely penetrant. This means that a dog can be genetically homozygous (at



risk) for the risk markers and still have normal hearing. This in turn means that many genetically at-risk dogs will not be identified or excluded from breeding by BAER testing.

An unbiased testing of a group of Dalmatians represented at a state specialty show in Australia revealed that the vast majority of the show dogs were heterozygous for the risk markers. This suggests that there is active selection to maintain the presence of the risk markers even while the use of BAER testing should reduce the prevalence of the risk version of the region. Work carried out as a student project suggests that it is possible that the protective markers at this site impact the external pigmentation on the dog such that the dogs with lower deafness risk have less pigmentation on their lips and nose. More work is required to test this (counterintuitive) observation but is beyond the scope of the current project. We expect to continue research on this important condition to identify functional changes associated with risk.