RESEARCH PROGRESS REPORT SUMMARY

Grant 02403-MOU: Microphthalmia and Delayed Growth Syndrome in the Portuguese Water Dog

Principal Investigator: Margret Casal, DVM, PhD

Research Institution: University of Pennsylvania

Grant Amount: $12,960

Start Date: 11/1/2017 **End Date:** 10/31/2022

Progress Report: End-Year 4

Report Due: 10/31/2021 **Report Received:** 12/16/2021

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Original Project Description:

Microphthalmia and delayed growth syndrome (aka "puppy eye syndrome") has been reported by Portuguese Water Dog breeders dating as far back as 1986. However, there is no information in the scientific literature and the majority of data concerning this syndrome has been obtained from records of breeders, which have anecdotal reports of the disease and little, if any, medical diagnostics. Affected dogs present with microphthalmia of varying severity, other eye abnormalities, short stature and other findings. To date, the investigators have been able to collect DNA from 24 affected dogs. Males and females can be affected, although females predominate (about 70%). Preliminary pedigree studies suggest an autosomal recessive inheritance. Human literature reports numerous syndromes associated with microphthalmia, and many genes have been identified as having a causative role. The goals of this investigation are to better characterize the clinical syndrome seen in Portuguese Water Dogs, confirm a suspected mode of inheritance, obtain additional samples for investigation into the genetic mutation, and develop a mutation based, genetic test for breeders to eliminate this syndrome from the Portuguese Water Dog breed.

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

Publications:

A publication presenting our findings is in preparation.

Presentations:

A poster describing our findings was presented at the Annual Faculty Retreat in Bryn Mawr, PA in 2019
A presentation for the Annual Association for Research in Vision and Ophthalmology in Baltimore, MD was prepared and was to be presented but because of COVID this most important conference was canceled.

Report to Grant Sponsor from Investigator:

Study Objectives
The objective of this study is to A) clinicopathologically and molecularly characterize microphthalmia with delayed growth in the Portuguese Water Dog (POWD) and B) develop a DNA-based test to assist breeders with their breeding programs and avoid producing affected dogs.

Results
Objective A is not complete due to the illness of one of the collaborators. However, we are finalizing a draft of the paper describing the clinical findings and the molecular defect. A paper was published about microphthalmia in POWDs recently by a group out of Cornell. However, this paper described only the ocular changes in affected dogs. With our publication, we will show that there can be other abnormalities such as low platelet counts and stunted growth, which makes this a truly syndromic disorder. We have also included pedigree analyses showing the autosomal recessive mode of inheritance. In the meantime, we have decided to put all of the clinical data into the final paper describing the disease-causing variant, making this a large landmark paper.

For Objective B, we received enough DNA samples from affected dogs and their relatives to perform an initial genome wide association study (GWAS). The DNA was sent to Illumina (Neogen) at the end of November 2018, and we received the results as expected in January 2019. We are absolutely thrilled with the results: A single, very significant peak was seen on the “Manhattan plot”, which allows us to locate not only the chromosome but the general area of that chromosome in which the gene must be located. Indeed, there is a gene in this area that, when mutated in mice and humans, causes a microphthalmia-like syndrome. We sequenced this gene and did not find a clear disease-causing variant. Thus, we submitted and sequenced the entire genome of one affected dog and one normal POWD. This allowed us to find a variant in a gene that is important for the development of the eye, and this variant is not present in any of the normal dogs including dogs of other breeds. We have made the test available to the breeders early in 2020 and have already tested 1,112 POWDs from at least 10 different countries to date. Of the dogs tested, 926 were tested as clear, 184 carriers, and 2 affected.