RESEARCH PROGRESS REPORT SUMMARY

Grant 02572-MOU: Characterization of Retinal Phenotypes and their Association with RPGRIP1 and Modifiers in English Springer Spaniels

Principal Investigator: Keiko Miyadera, DVM, PhD
Research Institution: University of Pennsylvania
Grant Amount: $99,303
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Original Project Description:

Advances in molecular techniques have led to the identification of nearly 30 gene mutations that cause inherited retinal diseases in dogs, often leading to loss of vision. While an insert in the RPGRIP1 gene has been linked to a blinding retinal disease first found in Dachshunds, this same mutation is very common in English Springer Spaniels (ESSs). However, retinal diseases are rarely seen in this breed, raising the question as to whether the RPGRIP1 mutation by itself causes retinal disease. Notably, the research team has found similar mismatches between the mutation and the disease in Dachshunds, where the disease presentation varies greatly. In this breed, they found additional genetic factors or ‘modifiers’ that together with the RPGRIP1 mutation, are better able to predict the disease. This study will determine if these factors or additional factors yet to be identified also contribute to retinal disease severity in ESSs by 1) clinically characterize the spectrum of the retinal disease in ESSs, including functional tests to detect the earliest sign of disease in dogs with an apparently normal phenotype, and 2) study the relationship between the RPGRIP1 mutation and the disease status and then search for other genetic contributors specific to ESSs. By determining the role of the RPGRIP1 mutation in ESS retinal disease, a reliable DNA testing platform may be established.

Funding for the research is provided through the collaborative efforts and generosity of the English Springer Spaniel Field Trial Association 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: None at this time.

Report to Grant Sponsor from Investigator:

A mutation in the gene RPGRIP1 has previously been linked to a severe form of inherited blinding disease known as progressive retinal atrophy (PRA) in Dachshunds. The same mutation has since been found to be widespread in the English Springer Spaniels (ESSs). However, whether this mutation affects vision in ESSs has been questioned as very little ESSs seemed to be diagnosed with PRA. Meanwhile, the ESS community has been DNA testing for this mutation, often making breeding decisions accordingly and hence potentially affecting the breed’s gene pool. The aim of our project is to clarify how the RPGRIP1 mutation correlate with the vision and retinal health in ESSs.

During the second quarter of the study, we continued to focus our research effort on collecting carefully ascertained phenotypic information and DNA samples from ESSs. We achieved this by carrying out fieldworks including I) National Specialty 2019 in California, II) National Amateur Field Trial 2019 in Illinois, and III) home visits to breeders in Washington state. To date, we have enrolled a total of 190 ESS dogs. Of them, 17 were afflicted with PRA, and all of which were RGPRIP1 affected. The average age at PRA diagnosis was 9.7 years which is considered among the most delayed-onset of PRAs known in dogs. While almost all the afflicted dogs were diagnosed at or above 7 years of age, there were younger dogs at around 4 years of age where the earlier signs of PRA could be picked up by careful observation for subtle changes in vision or by specialist examination.

Electroretinography (ERG) which can measure the activity of cells in the retina is the only way to pick up the very early changes before any clinical signs are picked up by observation or by eye exams. We have run ERGs in nearly 30 ESSs during this quarter. We find that most affected dogs demonstrate normal ERG traces when recorded at ages 2 years or younger. In older affected dogs, the measurement is more variable, ranging from mild reduction to complete loss. We hypothesize that some affected dogs carry a rescue gene/mutation or “modifier” that changes the course of the disease. The search for this modifier is one of the key aims of our study.

In the coming year, we will continue to enroll ESSs for the study by collecting clinical data and DNA samples. There is a particular need for enrolling more field ESSs as well as older affected dogs that are 3 years or above. We already have plans to participate in multiple regional specialties and field trials as well as in the nationals across the year. We will be performing ERG in additional affected dogs to get a better perspective how the retinal function varies across the different age range. Further, we will be starting the DNA chip and whole-genome sequencing experiments to search for the modifier gene/mutation that could be rescuing the affected dogs from going blind.

I look forward to continuing working with the ESS owners and breeders in the coming year – toward the goal of solving the question regarding the existing DNA test and find strategies to keep the Springers’ eyes healthy and visual, while preserving the precious genetic diversity of the breed.