RESEARCH PROGRESS REPORT SUMMARY

Grant 02248: Identification of a Novel Juvenile Myoclonic Epilepsy Gene and Its Underlying Disease Mechanism

Principal Investigator: Dr. Hannes T Lohi, PhD

Research Institution: University of Helsinki and the Folkhälsan Institute of Genetics

Grant Amount: $82,240.00

Start Date: 5/1/2016 **End Date:** 10/31/2017

Progress Report: Mid-Year 1

Report Due: 10/31/2016 **Report Received:** 10/28/2016

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Original Project Description:

Epilepsy is the most common neurological disease in dogs and affects almost all breeds. Genetics is likely to play a major role in seizure risk, and gene discovery remains as an important goal to better understand the disease and its treatment. However, genetic breakthroughs have been rare partially due to incomplete clinical diagnostics to identify true cases and controls, or to distinguish specific syndromes for genetic analyses. The investigators have recently utilized an advanced wireless video-EEG approach in clinical studies to identify juvenile myoclonic epilepsy (JME) in Rhodesian Ridgebacks with characteristic epilepsy phenotype, age of onset and photosensitivity. The pedigree established using the JME cases suggests a strong genetic contribution and is supported by preliminary genetic data that proposes a novel disease locus and a deleterious mutation in a neuronal candidate gene. These promising early findings necessitate further electroclinical and genetic studies for confirmation. In this study, the investigators' objectives are to: i) further characterize EEG, imaging and disease features of JME, ii) confirm the presence and segregation of an epilepsy gene, iii) investigate the breed-specificity, prevalence and penetrance of the mutation, iv) conclude the inheritance model, and v) define the pathogenicity of the mutation. The confirmation of the genetic defect would allow for development of a genetic test for breeding purposes and also to understand how myoclonic seizures develop. This could ultimately lead to improved treatments for canine epilepsy.

Publications:

Wielaender, F., Sarviaho, R., James, F., Hytönen, M. K., Cortez, M. A., Kluger, G., … Lohi, H. (2017). Generalized myoclonic epilepsy with photosensitivity in juvenile dogs caused by a defective DIRAS family GTPase 1. Proceedings of the National Academy of Sciences. http://doi.org/10.1073/pnas.1614478114

Report to Grant Sponsor from Investigator:

We have made a major breakthrough in our epilepsy study in the Rhodesian Ridgeback breed. We have utilized an advanced wireless video-EEG approach in clinical studies to identify a juvenile myoclonic epilepsy (JME) with characteristic phenotype, age of onset and photosensitivity. We have now also confirmed the discovery of a novel recessive JME gene and mutation in the RR breed. The entire study about clinical and genetic characterization has been submitted for peer review publication in high impact journal (PNAS, in revision). The confirmation of the genetic defect enables us to develop a genetic test for breeding purposes, and ongoing clinical and functional studies aim to improve our understanding how myoclonic seizures develop and how they could be better treated in future in the affected dogs.