RESEARCH PROGRESS REPORT SUMMARY

Grant 01901-A: Identifying the Gene Responsible for Dwarfism in Malamutes

Principal Investigator: Dr. Hannes T Lohi, PhD

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

Grant Amount: $12,960.00

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Progress Report: End-Year 1

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Recommended for Approval: Approved

(Content of this report is not confidential. A grant sponsor's CHF Health Liaison may request the confidential scientific report submitted by the investigator by contacting the CHF office. The below Report to Grant Sponsors from Investigator can be used in communications with your club members.)

Original Project Description:

The Alaskan Malamute breed suffers from a genetic skeletal condition referred to as chondrodysplasia. The condition has been extensively studied in this breed in the veterinary clinic during the 1970's and 80's. Affected malamutes have a disturbance in the process of endochondral ossification, which results in short stature and curvature of the front limbs. The disease is thought to be inherited trough a single gene, in an autosomal recessive manner. The molecular genetic background of the disease is yet to be identified, and the aim of this study is to identify its genetic cause. Our research group has previously identified a mutation that causes chondrodysplasia in the Norwegian Elkhound. Although both breeds suffer from similar recessive condition, the genetic cause is not the same in Malamutes. We will use two complementary research methods to discover the causative mutation: exome sequencing and genome-wide association mapping. The identification of the causative mutation would enable us to develop a genetic test for breeding purposes, and it would help us to understand how the disease develops in both dogs and in human.

Report to Grant Sponsor from Investigator:

In the Alaskan Malamute chondrodysplasia study, we have been using two complementary research methods to discover the causative mutation: exome sequencing and DNA-marker-based genome-wide association mapping. Thus far we have analysed genome-wide data from ten affected dogs and up to 87 healthy control dogs. Part of the control cohort was obtained from a previous cataract study. The Alaskan Malamute chondrodysplasia is thought to have an autosomal recessive mode of inheritance and we have performed our data analyses under this model. We have now identified a chromosomal region that shows association to the disease. This region was identified by using several different genome-wide analysis approaches, which included both basic case-control association and family-based methods. The finding is still tentative because our sample cohort has some issues concerning unwanted population structure. The affected dogs form a separate cluster from the control samples, which means that they come from a separate line of dogs than the control dogs. This population structure can have an effect to the results by introducing false positive findings that are caused by the population difference and not by the difference in affection status. To correct this problem, we have recently genotyped a new sample set of seven affected and seven control dogs but unfortunately half of these sample failed because of their poor quality. We have previously performed exome sequencing to one carrier dog and two affected dogs, and now we are in the process of sequencing four additional affected and two additional carrier dogs by using an updated exome sequencing platform.

The main obstacle in this study has been the availability and quality of samples. Many samples of affected dogs have been received as old DNA samples that have had both low DNA-quality and quantity. Furthermore, control dogs that are closely related to the affected dogs have been difficult to obtain, and this has caused the problems in population structure. Consequently, any new samples from affected dogs and their relatives would be greatly appreciated. However, people within the Alaskan Malamute breed have been extremely supportive of the research project, and we wish to warmly thank all who have contributed to the study and helped us in obtaining samples.