UNIVERSITY OF CAMBRIDGE
Department of Veterinary Medicine

MPhil Project: Identification of the genetic variant that causes Spongiform Leukoencephalomyelopathy (SLEM) in the Border Terrier dog breed

Start Date: 1st October 2024

Supervisors: Dr Cathryn Mellersh and Dr Lisa Alves

This project will be undertaken within the Department of Veterinary Medicine at the University of Cambridge and is an exciting opportunity for a student to learn a wide range of genetic and molecular biology techniques, including whole genome sequence analysis, variant filtering and relevant techniques to investigate gene expression changes. Our expectation is that data generated during this this project will also result in a peer-reviewed publication.

The overall aim of the project is to identify the causal genetic variant for spongiform leukoencephalomyelopathy (SLEM) in Border Terriers, develop a validated selective breeding tool and improve our understanding of the aetiology of this disease. The disease was first described in 2012, in a 3-week-old male Border Terrier puppy in the USA (P. Martin-Vaquero et al. 2012) and more recently, clinical, electrophysiological and imaging features of the disease have been described in UK Border terriers (R. Gutierrez-Quintana et al. 2019), indicating this disease is widespread globally.

The Canine Genetics Centre has previously generated whole genome sequence data from Border Terriers affected with SLEM, and from healthy dogs of the same breed, and has identified a deep intronic, single-base substitution in a strong candidate gene, that in the homozygous state is significantly associated with SLEM in Border Terriers (unpublished data). This unpublished variant is the target of a commercial DNA test used by dog breeders to inform their breeding decisions (https://www.cagt.co.uk/product/slem/).

However, the previous WGS analysis made use of the canine reference genome available at the time, CanFam3.1, in which there are multiple gaps approximately 40 kb upstream of the candidate gene. In addition, a thorough search for structural variants that might be involved in the disease was not undertaken. We therefore cannot exclude the possibility that the candidate variant identified previously is a benign variant that is simply in linkage disequilibrium with the true, as yet unidentified, causal variant.

The successful student will therefore utilise the existing whole genome sequence data to confirm and validate the SLEM causal variant, undertake experiments aimed at understanding how and why the causal variant causes SLEM and develop a validated DNA test that will offered commercially to breeders to help them eliminate this fatal inherited disease from the Border Terrier breed.

Specific objectives are as follows:

1. Align our existing whole genome sequence (WGS) data (from five cases, two obligate carriers and three controls) to newly released canine reference genome(s) and to WGS of multiple different breeds from our in-house, collaborative and consortium datasets (over 1000 WGS) and use our in-house bioinformatics pipeline to filter variants and identify candidate causal variants.

2. Genotype all candidate causal variants (Objective 1) in our large, existing cohort of Border terrier samples, (including known cases, obligate carriers and older unaffected dogs), to exclude all variants that segregate inappropriately (for an autosomal recessive, early onset, fatal disease) identify causal variant and estimate frequency in Border terrier populations.

3. Compare post-mortem tissue from affected puppies and age-matched controls to investigate changes to the expression relevant genes and proteins, likely using western blot and quantitative PCR analysis.

4. Develop a genetic test, based on the causal variant, to be offered by Canine Genetic Testing at the University of Cambridge (https://www.cagt.co.uk/).

5. Publish findings in a peer-reviewed scientific journal.

Funding: Fully funded by BSAVA, includes stipend of £19553 pa and University fees at the home rate.

How to apply: Contact the Supervisor to discuss the project before submitting an official application. More here on application process here: https://www.postgraduate.study.cam.ac.uk/courses/directory/cvvtmpvet