REPORT OF CECS/PGSD BRIEFING MEETING

FEBRUARY 15TH 2018

A briefing meeting was held at the Animal Health Trust on February 15th 2018, to outline plans for a project aimed at identifying regions of the genome associated with Canine Epileptoid Cramping Syndrome (CECS) / Paroxysmal Gluten Sensitive Dyskinesia (PGSD) in the Border Terrier.

Those invited to attend had included

- Representatives of the group which had raised considerable funds for the Animal Health Trust through social media and a Justgiving Page
- Members of the Border Terrier Breed Health Group
- Health Representatives from the seven UK Border Terrier breed clubs and the Swedish Border Terrier Club.

Presentations were given by Sally Ricketts and Chris Jenkins of the AHT Canine Genetics Group at the Kennel Club Genetics Centre, and Mark Lowrie (RCVS & ECVN) who is a veterinary specialist in neurology.

THE PROJECT

The plan is to conduct a collaborative project aimed at identifying regions of the genome associated with PGSD by performing a 'Genome-Wide Association Study' (GWAS), also known as a genome scan.

To ensure optimal efficacy, the GWAS is planned to use dogs from a tightly defined clinical definition of the disease, including only CECS-affected dogs that are sensitive to gluten as affected examples (cases) , and carefully selected unaffected examples (control samples)

A study previously carried out by Mark Lowrie has linked CECS to gluten sensitivity and Gluten sensitive CECS has now been named 'paroxysmal gluten sensitive dyskinesia' (PGSD).

Mention was made of a recent overseas study aimed to identify genetic variants that might contribute to the development of CECS. This had been carried out using DNA samples collected from Border Terriers in Finland, The Netherlands, and Germany. This investigation included a GWAS that tested thousands of markers across the genome, but it had been unable to identify any regions of the DNA associated with the disease. It was thought that this may have been because the dogs included had been from different countries, had included a wide range of clinical features, and had relied on owner-reported signs as opposed to clinical diagnoses. It was thought that this broad definition of cases may have been the reason that the Finnish study had been unable to identify any associated regions of the DNA.

The present proposed study would attempt to eliminate as many of these drawbacks as possible, by carrying out a more focused study including only CECS-affected dogs that are sensitive to gluten as the cases, and carefully selected unaffected dogs as control samples.

The first objective will be to collect cheek swab samples from a minimum of 100 well-defined PGSD cases and between 100 to 200 unaffected controls.

SAMPLES REQUIRED

Work is currently going on to provide a clear, yet simple, definition of precisely what dogs will be required as case samples and what as control samples. Collecting a tightly defined sample set will be crucial to giving the best likelihood of successfully identifying regions of the DNA associated with PGSD.

When these definitions have been clearly defined and agreed, the cases and controls for the study will be recruited through the Kennel Club, the Border Terrier breed clubs in the UK; and via an appeal in the veterinary media. For this study, only UK based dogs will be used, all of them descended from current UK lines. A brief questionnaire will be used initially to determine that affected or unaffected dogs are suitable for inclusion in the study and for affected dogs, video footage of a typical episode will be requested to enable as accurate a diagnosis to be carried out on each affected dog to be used. For unaffected cases to be included in the study confirmation will be required that they are not on a gluten-free diet. Owners of affected dogs fulfilling the above criteria will then be asked to have their dogs tested for the currently recommended serological tests for PGSD. The results will be reviewed by Mark Lowrie to confirm that they can be used in the study.

An full application for ethical approval from the Royal College of Veterinary Surgeons for this research will be submitted by Mark Lowrie to enable the serum sampling to be carried out.

COSTS

The costs for the initial sample recruitment for serological blood tests (affected cases only) is estimated at ~£10K with swab test costs for the unaffected cases estimated at ~£2K. So, Phase 1 to obtain the required samples is estimated at ~£12K.

This will be more than covered by the funds currently held by the AHT and provided by Just Giving and Social Media donations.

Once the samples have been organised, a further ~£36K will be required to carry out the GWAS and another ~£4K to carry out Whole Genome Sequencing of two cases – total ~£40K.

It was hoped that some of this £40K will come from additional Social Media funding, some from the Border Terrier Breed Health Group Fund (contributed by the clubs for Border Terriers and other donors), and some from other sources

The total time to complete the project may be anything up to 3 years.

ARISING FROM QUESTIONS

Arising from questions raised at the briefing the following points were noted:

- It was estimated that roughly 90% of Border Terriers affected by CECS are gluten sensitive and do respond favourably to a gluten free diet.
- The genetics of CECS/PGSD is likely to be complex with multiple genes associated with the disease.
- Therefore, there is no certainty that the planned study will successfully identify regions of the genome associated with PGSD.
- Even with a successful outcome for this phase of the study, the available advice to breeders may not be of a clear black and white nature. It may simply be indicative and give statistical probabilities of what may result from various breeding combinations of dogs
- Great care will have to be taken in the selection of affected case dogs and unaffected control dogs.

NEXT STEPS

The next moves will be:

- Obtaining RCVS final Ethical approval for the serological testing to be carried out by Veterinary Surgeons.
- Production of clear and simple definitions for required sample dogs, to be used to recruit affected cases and unaffected control dogs.
- Sample recruitment over an 18 month period
- Application to Breed Health Group for part funding
- Application to other potential external funders
- Carrying out of the GWAS and then whole genome sequencing.

The AHT was asked to report on progress regularly – say three monthly - even if only to give a brief update of progress on sample recruitment etc.

CONCLUSION

There was considerable enthusiasm to proceed with the project but with realistic recognition that there were no guarantees of success and that specific clear ‘black and white’ advice for breeders may not inevitably follow even a relatively successful first phase, in fact for a complex genetic disease a simple SLEM like test is extremely unlikely.

It may be that it will be possible to develop a genetic risk score based on a number of genetic regions, with utility similar to the EBVs used for Labrador Retriever hip dysplasia. Importantly, the study could lead to an improved biological understanding of the disease, which may help with the development of possible preventive therapies or treatments.

PRESENT

Present at the Briefing were:

PROJECT TEAM

Genetics	Sally Ricketts, Chris Jenkins
Neurology	Mark Lowrie

BORDER TERRIER COMMUNITY

Michelle Barnett, Jan Gale, Dr Andy Harbottle, Mike Hollingsbee, Ronnie Irving, Janet Lee, Loulou Troupe, Chris Wallace, Tony Wrenn

RI/February 21, 2018