Canine Genetics Research Progress Report

Idiopathic Epilepsy in Keeshonds

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Why do we need this research?

For many years, Keeshond owners and breeders across the world have been working with scientists and clinicians towards the goal of uncovering the genetic basis of idiopathic epilepsy in the breed. Dogs are diagnosed with idiopathic epilepsy if they have recurrent seizures for which no cause can be identified. As in several other breeds, this primary form of epilepsy appears to have an inherited, or familial, basis in the Keeshond. Previous research has suggested that the mode of inheritance in the Keeshond might be autosomal recessive, but the pattern remains unclear. Familial epilepsies in the dog have so far proved difficult to characterise at DNA level; the main reason being that multiple genes are likely to be involved. Geneticists usually need to analyse large numbers of DNA samples before they can begin to unravel the mechanisms underlying these complex polygenic conditions. A further complication of idiopathic epilepsy studies is that a diagnosis is not always reached as easily as you might think; seizures in an individual dog can result from a number of underlying causes and, ideally, all possible causes are excluded before a dog can receive a robust diagnosis of idiopathic epilepsy. Despite these and other challenges, Keeshond owners have helped us to build up a sufficiently large collection of DNA samples from epilepsy affected and unaffected dogs that we are at last ready to take the next step in this research.

What does the research involve?

The Animal Health Trust (AHT) is working with Dr Barbara Skelly, a veterinary surgeon at the University of Cambridge in the UK, to investigate idiopathic epilepsy in the Keeshond. Our ultimate

aim is to develop a robust DNA test that Keeshond breeders can use as a tool to inform future breeding decisions. We still have a long way to go, but we are pleased to report that we are ready to go ahead with an in-depth genetic analysis known as a "genome-wide association study". DNA samples will be sent to a specialist laboratory which uses state-of-the-art genetic marker arrays to generate data that we will examine closely here at the AHT. We will compare thousands of DNA markers from dogs affected by epilepsy ("cases") with those from unaffected dogs ("controls"), looking for one or more regions of the genome that are consistently shared between cases, but not with the controls. Should we find evidence of one or more promising regions, the second stage of our project, known as "fine-mapping", will seek to identify candidate genes within these target regions that we can explore for DNA sequence errors that might be responsible for epilepsy.

Do we have enough samples?

The enthusiastic participation of Keeshond breeders and owners worldwide means that we are ready to submit samples from around 24 cases, alongside a similar number of controls, to the specialist laboratory for genome-wide scanning. The exact number of samples we send to the laboratory rests on a final quality control step. We have already carried out stringent quality checks on all our samples, as the microarray technology requires exacting levels of DNA quality and quantity. The majority of our samples reach these high standards, but some drop below the threshold for suitability. These samples will not be wasted; they can be used in further experiments in our own laboratory at the AHT should we identify one or more regions of DNA that can be looked at more closely.

When will we get the results?

The genome-wide scan, and analysis of the large volume of data it will generate, is likely to take several weeks to complete. We hope to make preliminary results available to the Keeshond community by the end of January 2013. Our ideal scenario is that the scan yields compelling results that are robust enough for us to proceed to fine-mapping. However, as mentioned earlier, previous attempts to characterise the genetic basis of epilepsy in dogs suggest that this condition is complex.

We should be prepared to acknowledge that the number of samples in this set might to be too small at this stage to pinpoint regions of interest that we can follow up with any confidence. Should this be the case, our only option will be to collect more samples and carry out another genome-wide scan in the future to add to our data.

Can more be done to help this research?

Whether or not we meet with success in this first stage of our study, we encourage you to continue to send us DNA from any Keeshond unfortunate enough to receive a diagnosis of idiopathic epilepsy. It helps us considerably if you can include as much clinical information as possible with your submission. We also welcome samples from older Keeshonds, aged eight years or over, who have never shown any signs of epilepsy - to use as controls in our study. Keeping us updated on changes in the health of any dog we already hold a DNA sample from also helps us tremendously in our continued research. For further information on how to submit a sample, or to send us updated health information, please email Bryan McLaughlin at **bryan.mclaughlin@aht.org.uk**

We would not be entering this exciting phase of our study without your continued support. Our grateful thanks go to all those owners and their Keeshonds who have contributed to this project over the years. Particular mention must be made of both Anji Marfleet and Jane Saunders for their invaluable help; their impressive knowledge of the breed worldwide has been a real asset to our research. We wish to thank Dr Barbara Skelly and the Kennel Club Charitable Trust for arranging funding for this study - without them this work could not proceed.