Glaucoma Research Update

Following on from Kathie Kinton's recent report to the Border Collie Breed Council what follows is a summary of the research so far from the leader of the research team at the Roslin Institute, Professor Kim Summers, and well worth reading in full before reading the rest of this posting.

Goniodysgenesis and glaucoma: recessive vs polygenic inheritance.

There are a number of models to account for conditions that are clearly heritable (run in families). Firstly if the condition is dominant, affected offspring would always have at least one affected parent. Two affected parents could have affected and unaffected offspring. If the condition is recessive, two unaffected parents can have affected offspring but if both parents are affected all offspring should be affected. Finally if the condition is polygenic (ie several – many genes involved) there will be a familial clustering of affected individuals but there will not be simple patterns of inheritance. For example, with hip dysplasia, on average two affected parents may have about one third unaffected offspring, which does not match either single gene model. The implications of these models for breeders are different.

1. Dominant

This is easy to breed out as it is just a matter of avoiding breeding from any affected individual. However, we believe this in unlikely to be the case for goniodysgenesis or glaucoma, since there are cases where neither parent was affected and yet one or more of the offspring have failed the test.

2. Recessive

The problem here is that the undesirable genetic variant can "hide" for generations. We all inherit two copies of every gene and for a recessive the good version masks the presence of the undesirable version. Two individuals with a common ancestor can both be carrying the undesirable variant inherited from that ancestor and when mated their offspring have a 1 in 4 chance of inheriting this from both parents and hence being affected. This is why we would always recommend not mating closely related individuals. As the number of generations from the common ancestor increases the probability that both parents carry that variant decreases so the chance that two related individuals are both carriers decreases. However, that possibility is always there when the animals have a common ancestor, however far back. The data we have are largely consistent with a recessive model, although we know of situations where two affected parents have apparently had one or more unaffected offspring. At this stage we can't tell from the databases whether this is due to failure to report a fail, lack of testing of the litter or the diagnostic uncertainty of having the test done by different people. Therefore we are reluctant to say that goniodysgenesis is recessive, but clearly breeding relatives (even if unaffected) would not be desirable.

3. Polygenic

In the polygenic situation, the disease is determined by a number of different genes. An affected individual has had to inherit the risk variant for all of these from one or both parents. The chances of this decrease as the individual gets further from a case of the disease. In this case perhaps one could consider breeding distant relatives who have no incidences of the condition in their families, including aunts and uncles, distant cousins etc, not just the direct lines, for several generations (the more generations free from the condition, the better, but certainly at least four). The family structures we have seen for the Border Collies in our study are consistent with this polygenic model (because there are no real predictions about inheritance patterns).

This summary largely echoes the advice that was received from Aimee Llewellyn, who also stressed that using older dogs who are unaffected is safer than using young dogs, if goniodysgenesis and glaucoma are progressive and develop as the dog ages. In summary (in her words): "The best-case scenario is to seek out, and pair up those dogs with the widest number of close relatives (parents, siblings, progeny) ***who are unaffected****." I would add that it would be even better to use animals who have no affected relatives in several previous generations. This could be based on both goniodysgenesis and glaucoma, but it would be particularly important to avoid animals who have relatives with glaucoma.*

Since goniodysgenesis is quite prevalent in the Border Collie population at the moment, avoiding breeding from all individuals who have failed the BVA gonioscopy test could result in reducing the breeding pool of dogs and hence the genetic variability in the breeding population. The problem here is that the undesirable version of other genes may end up at higher frequencies and lead to other health issues. So it is important to use as wide a variety of animals for breeding as possible.

These thoughts are intended to provide background information for decisions about breeding strategies that may reduce the risk of passing on goniodysgenesis and the predisposition to glaucoma. Without a specific genetic test for the single or multiple genes involved we can't guarantee that puppies produced following these ideas will be free of goniodysgenesis and glaucoma, but could reduce the incidence in future generations.

Sadly, the latest peer review has been turned down – there were concerns expressed by the review panel about the number of eye panellists used and the fact that two results were changed on second testing – as far as we are aware this was the only time this has happened and we can assume that test results ARE valid.

In addition the reviewer had concerns that the data was worldwide and again a number of Vets were involved with the testing results.

Going back to the early days of the group CEA research was carried out, and achieved a DNA test, using data gathered from using eye panellist results – it would

seem perfectly reasonable therefore to assume that using results of gonioscopy tests carried out by in many cases the SAME panellists would be an acceptable way forward.

It has not been an easy path for us to tread trying to find out WHY Glaucoma reared its ugly head in the Border Collie breed and how it is inherited – it now looks increasingly likely that the inheritance of narrow angles is different to the inheritance of glaucoma. The results clearly show however, that it is inheritance is not dominant as confirmed by Prof. Summers.

We have found it very hard to get DNA samples from as many dogs as the researchers would have liked, both here in the UK, Europe and Australia – despite numerous requests. Thanks must go to those that have provided DNA samples.

Researchers can only work on what they have and if the samples are limited it makes the work doubly hard.

Since Alan Wilton wrote his paper on the subject and the study was passed over to Roslin as recommended by Alan the study had three aims. Firstly to look at the pedigrees and see if there was evidence that goniodysgenseis is inherited. That part of the study has been completed and confirmed that it is inherited. The risk factors of lines that can be bred from is outlined above.

Secondly, there was a need to disentangle the relationship between goniodysgenesis and/or glaucoma so that a genetic test could be developed. This is the area that requires further research in light of the recent research paper.

The researchers are therefore looking at the 75 plus dogs, about half affected with goniodysgenesis and then a separate analysis of the dogs that have gone onto lose eyes due to the glaucoma.

Going forward the geneotyping study will analysis the results. The researchers have asked for any owners that have not submitted DNA if they would be willing to do so as this will both assist the geneotyping and the development of a genetic test either directly by Roslin or working in partnership with others.

They need DNA for any dogs that have failed the gonioscopy and even more importantly the DNA for any dogs that have lost eyes due to glaucoma. Close relatives and sire and dam's DNA would be of great value to the research to move it onto the next stages and back to the reviewer.

If anyone has results that are not on the database or "missing" information on the database it would be appreciated if you would kindly take a little time to complete. In addition, if any of you have had your dog's re-tested and your entry shows only one result could you email us the date and the name of the vet that did your second

and in some cases third test. This will help when the data is submitted again to the reviewers. We know for example that some dogs were tested at the testing days and received the same results demonstrating the reliability of the data and the BVA Vets.

As many of you are aware the research is being funded by the Dog Trust but this only has 6 months left to run we will of course support any application for further funding. DNA sent now might make all the difference.