

Epilepsy in ISDS Border Collies

„Definition of responsible genes as first step to a gene test by complete genome scans of affected ISDS Border Collies and related dogs, and development of a practically usable breeding estimation program to predict the risk of epilepsy in a planned mating“

This is the title of the Vet. PhD work of Gitte Anders, long time member of the ABCD and dedicated sheepdog owner, and responsible scientist in the international workgroup including the coordinator Prof. Gerald Reiner (German Vet. Genetist) and Prof. Schmidt (German Vet. Neurologist) Prof. Leeb (Swiss Dog Genetist) and Prof. Lohi (Finnish Epilepsy Genetist).

Because the Border Collie populations of ISDS, Kennel Club, FCI and unregistered pet Border Collies have genetically grown rather far apart, it is very difficult to search for single gene differences between individual dogs without getting lost in the otherwise different genetic make-up. In other words, it is easier to find needles in a hay-bale than in the whole haystack. This fact is the main reason why we concentrate only on our ISDS working dogs.

Introduction

Epilepsy is becoming the most important genetic disease in Border Collies. From a formerly rare condition this debilitating disease has developed into a rather common one in our breed. Border Collies are among the leading breeds in occurrence statistics of veterinary neurologists, and due to a breed related therapy resistance, very hard to treat. The average survival rate of young Border Collies with general epilepsy is less than a year in spite of aggressive treatment.

Why epilepsy?

Genetic diseases should be ranked according to their importance for the individual dog and the breed. This means deadly or debilitating diseases, which compromise the working ability, are more important than diseases which can be easily treated or are very rare.

In contrast to that, the public perception, especially in the social media, seems to be strongly influenced by the fact of whether a gene test is available or not. Unfortunately, the new gene tests (IGS, TNS) are just byproducts of scientific work on human diseases for which the few ill Border Collies were role models. They serve to get some financial return. The fact that there is a gene test does not mean, that these diseases are very important for

the breed. This can be, but it need not be. The importance of TNS is very low, the one for IGS needs further observation, but since IGS still occurs less often and is easily treatable, it is not of such consequence as epilepsy. PRA is totally rare nowadays, and with CEA even most DNA affected dogs will not go blind, and the gene test does not show coloboma as we know now. Unfortunately, the validity of gene tests (at least in the USA) is not controlled by any governmental body but due to patent legislation is solely based on private knowledge. Same applies for the question whether the tested gene really is the only one causing the disease.

With epilepsy the scenario is totally different. Affected dogs lose their working ability and 9 out of 10 young epileptic Border Collies die in a few months time. So, we don't have a gene test (yet), but we have a problem.

Is epilepsy truly a genetic disease?

Epilepsy in dogs has been proven beyond any reasonable doubt to have a strong genetic influence. The disease is more prominent in affected families with relations living under totally different environmental conditions. The same applies for many forms of human epilepsy. For some dog breeds genes have been defined.

Known carriers of epilepsy can be followed over generations in a pedigree of an affected dog.

In contrast to simple monogenetic diseases epilepsy in most dog breeds is influenced by about 10 gene pairs, all of which can be dominant or recessive. The usual working hypothesis is that there are some major genes (usually recessive) and some operator genes, who work like a switch turning the operator genes on, off or modifying their level of expression.

What about other reasons for fitting?

Of course, there can be reasons for epileptic fits other than a genetic cause. The most likely is a severe head trauma, but Hypothyreosis, Liver shunt, intoxications and others have been named. If fits are just a byproduct of an underlying disease, a) there will be more symptoms of this disease and b) they will stop when the disease is treated.

Unfortunately, Border Collies usually just fit and don't show any other symptoms, but are perfectly healthy dogs in between fits and even with the most thorough diagnostic procedures usually no underlying disease can be found in Border Collies. This refers to the classic cases of a young Border Collie starting to fit.

Generally, the lack of evidence for primary causes in all dog breeds has led to changed diagnostic requirements in veterinary neurology for diagnosing inherited epilepsy. Since pathological changes in the brain of epileptic dogs are only visible in an MRI in under 2% of the cases, this is no longer a requirement for dogs under 6 years. Heart x-rays and other diagnostic procedures proved equally ineffective, so that nowadays a neurological examination and a full blood check is enough to diagnose genetic epilepsy.

Is epilepsy a problem in Border Collies?

If anyone asks a veterinary neurologist, which disease they would fear most, they would probably answer „Epilepsy in Border Collie“. Together with Labradors and GSD, Border Collies lead the statistics of epileptic dogs. This runs through all studbooks and even applies to unregistered Border Collies. Australian Shepherds, who are a related breed, are also severely affected.

What makes the Border Collie special, is that often therapy is not working. The MDR transport protein, which serves as pump between blood and brain fluid, tends to be overexpressed = overactive in Border Collies. So, more often than not, it is impossible to get a high enough drug level in the brain to prevent further epileptic fits, even though the blood level is so high that the drugs cause liver or kidney problems and cannot be raised further.

Is it a problem in ISDS Border Collies?

Epilepsy seems to be a growing problem in ISDS dogs as well. From very few affected dogs in the past, there seems to be a steady rise in occurrence.

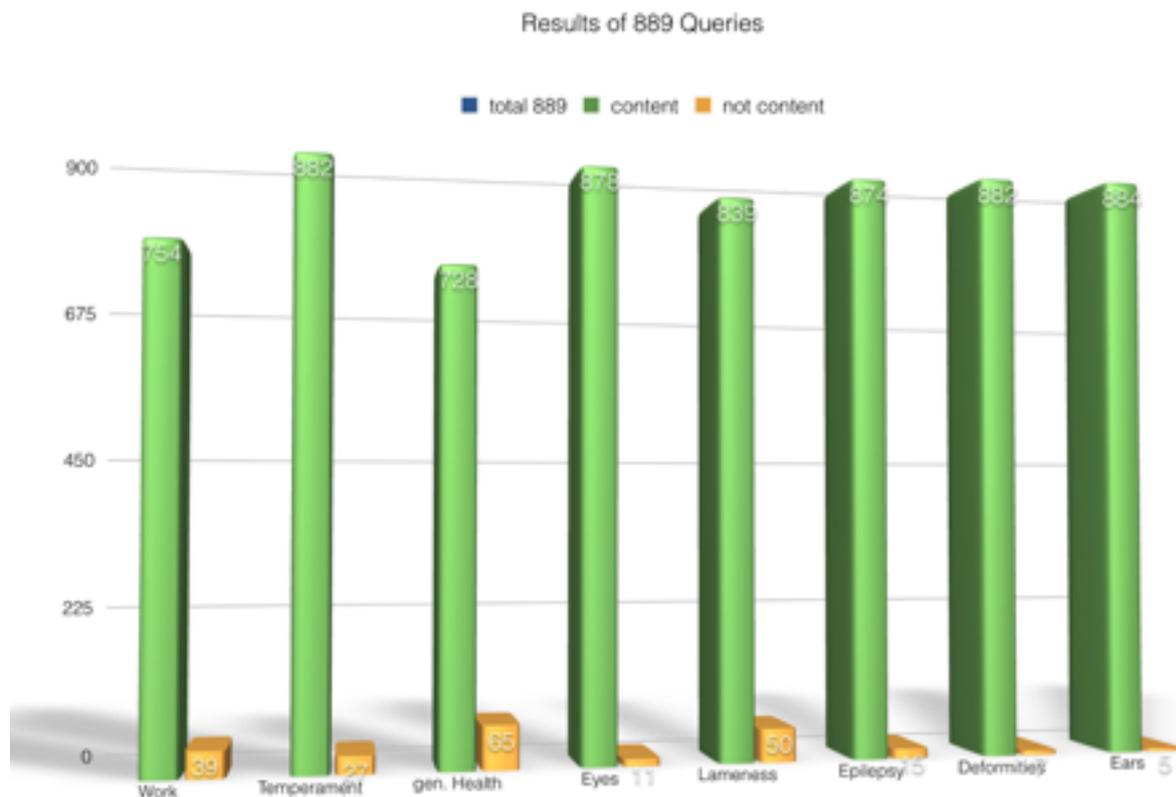
This is in accordance with the fact, that polygenetic diseases (diseases, or better dispositions, which are influenced by more than one gene) will occur more often when the relationship percentage in a breed rises. Then, the recessive genes will meet more often and detrimental dispositions will show more often. In a closed breed, with no new genes coming in, after about 100 years this is expected to happen. The use of popular stud dogs is going to speed up the process, especially if one of the popular stud dogs happens to carry many defective genes.

Epilepsy in ISDS dogs

For a number of years now, I have done statistics about the major diseases for the ABCD AGMs. For most diseases in our breed there are multiple publications about the possible genetic background, even though the actual mode of inheritance often is not clear. Usually, it is not as simple as the sellers of gene tests make it sound.

To get reliable numbers to start with, in 2012 we (the ABCD breeding committee) organized a survey of all ISDS dogs from ABCD members. We sent out a short questionnaire for every single dog enquiring about the owner's contentment with working ability, temperament and physical health of their dogs. To get a decent return rate we included prepaid and pre-addressed envelopes, a system which did work quite well. From 1393 sent out questionnaires we got 889 back. It cost about 1500 Euros in material and postage, labour is always done on an honorary basis, which makes these things possible for a rather small society.

The results were as follows:



These results were rather encouraging as the overwhelming majority of dog owners were content, still we kept an eye on the named problems. Epilepsy seemed to crop up more often with time, so we started a register to get an idea with which size of problem we had or didn't have. The problem seems to be not catastrophic, but still big enough to be a potential danger for the breed's future. We started an official register, in which only proven cases were taken. All health information about individual dogs is available members on the members-only section of our website.

The total of epileptic dogs that were brought to our attention voluntarily by their owners or breeders is stated in the table below. The foreign dogs are all published in some epilepsy data bases.

All of these numbers will obviously represent only a certain percentage of epileptic Border Collies, because breeders usually don't like these things to go public and they often try to prevent it.

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| Publicly known epileptic dogs in the ABCD | 61 |
| Publicly known epileptic dogs before 2006 | 9 |
| Published epileptic dogs in other countries | 220 |

Sweden alone has 98 epileptic affected dogs published in their studbook, who all go back to

imported ISDS dogs. They seem to be especially unlucky, since they imported a lot of one very successful dog and line bred back to him, and the offspring of this great dog, unfortunately, revealed him as a major carrier of epilepsy genes.

In the UK it seems to be rare. Still, if one asks without spreading hysteria, there is an impressive number of persons who knew fitting ISDS dogs, and there are quite a few UK dogs among the 220 published ones.

It is absolutely unthinkable, to ban parents or relations of epileptic dogs from breeding, because the number of dogs would be much too high. It would include some of the best breeders and would have a very detrimental effect on the genetic diversity of the breed. The genes seem to be extremely widely spread, and at the moment there seem to be very few lines of exported dogs without any affected offspring. The 61 known dogs in Germany were bred by 44 different dogs and 48 different bitches. The tighter the line breeding on before unknown carriers the more affected dogs can be expected. We had one litter with 3 affected out of 5 pups and one with 5 affected out of 10 pups. Those are the worst examples, and in retrospective these were matings which could have been avoided, if the knowledge about carriers had been available.

With a polygenetic disease there is no way to predict how many deleterious genes an individual dog may carry, unless there is offspring to evaluate. It is a huge difference whether a stud dog has a few affected offspring out of hundreds of pups or whether he breed 8 epileptic dogs with 3 different bitches and only 24 pups in total.

The only way to prevent the spreading of the genes is preventing too many of them meeting in pups, endangering the individual dog and concentrating the genes in the breed. The only way to do that is to educate people that it is vital to be open about diseases in the safe knowledge that it happens to everyone and does not mean the breeding is bad.

In the ABCD we tried to encourage people to be open about the disease, because, as mentioned before, knowledge about potentially risky matings is the only way to prevent them. Even if there are overruling arguments to do a risky mating because dog and bitch fit superbly work wise, informing the pup buyers about potential risks is in the best interests of breeders. With the new EU liability legislature breeders will be held more and more accountable for „defects“ in the dogs they bred. The only way around that is information of the buyers before they buy. The liability clauses are only valid for hidden faults, if the buyer is aware of a risk the seller is not responsible anymore.

The PhD study

Everyone dreams about a gene test for epilepsy in Border Collies, but all attempts to find the responsible genes have been unsuccessful in the past.

The first reason for this is, that the used genome scans never were really complete and did not include the vast amount of operator genes, but only checked the actual protein encoding gene sequences (Exon scan). The second reason is that too many variables were in the equation to get a definite result. Border Collies from all kinds of studbooks were

compared, plus there are quite a few different forms of epilepsy, which are determined differently. Everyone looking at a Border Collie in a show ring, knows that it is nearly a different breed to our working sheepdogs. Then, there is a genetic drift in different continents due to different priorities or show fashions, and again all will be genetically different to ISDS Border Collies.

If one tries to find out differing genes in the genomes of different dogs, it is vital that the dogs are related enough so that their genome is fairly the same and only a small percentage of genes are different, with hopefully the disease causing genes quite prominent among them.

These are the reasons why we want to concentrate on ISDS Border Collies, and among the epilepsy forms on the most dangerous epilepsy form, the classic juvenile generalized epilepsy.

The objective of the study is to compare the genes from related litters, from one of which one or preferably dogs got ill with the above mentioned epilepsy form. This will not be easy, and we will need to publish what and which dogs we are searching for. Since Gitte will do the full genome scan (protein encoding genes and all operator genes) which is highly complicated and very expensive, only a small number of tests will be possible. One of the most modern machines for this procedure is situated at the Munich university and due to the good connections of Prof. Reiner to the Munich genetics faculty, Gitte will be able to use this machine at the lowest possible costs. Unfortunately, such a really full genome scan will still cost 1.000 € each. The research group hopes to find at least some of the major genes for epilepsy in Border Collies. The identification is the most difficult step. If that can be achieved, a gene test is in easy reach. That would give the breeders a powerful tool to avoid matings with a high risk of epilepsy, which would be a dream come true for many breeders, and anyone supporting such a goal would have a high profile in the dog world.

In addition to the genome project, Gitte is accumulating information about fitting Border Collies and feeding those into a breeding evaluation program. This program is normally used for the breeding evaluation of farm animals, and it has proven highly efficient in the selection for genetically determined traits without knowing the actual genes. Milk production is the best known feature, but hundreds of traits are being estimated and selected in bulls, cows, rams and other breeding stock. So, by feeding information about parents, siblings and offspring into the computer an estimation about the genotype determining a certain trait can be given. Thus, breeders can get an evaluation of planned matings in view of an intensification of a trait (f.i. milk fat) or the avoidance of a trait (f.i. epilepsy). The more information is available the more accurate the risk assessment will be.

To prevent the spreading of genetic diseases in a dog breed it is vital not to pair two carriers of a risk together. Even if a gene test for epilepsy will not be possible due to lack of suitable samples, the breeding evaluation program alone will still be a major step forward in dealing with this crippling disease.

Conclusions

- Epilepsy in Border Collies is a growing problem.
- It is a debilitating disease, in the case of the juvenile generalized form, killing the dogs in a few months in spite of treatment.
- An underlying breed specific genetic disposition is proven.
- The numbers of affected dogs seem to rise, and it is a reason of growing concern among Border Collie owners and veterinary neurologists.
- As breeding society we have a responsibility to look after the health of our breed.
- Attempts of finding responsible genes were unsuccessful up to now, because genome testing is very expensive, and because samples from too far related Border Collies and with too many different epilepsy forms were compared.
- The described scientific study only deals with working ISDS Border Collies.
- The goal of giving breeders a tool to avoid this disease among their dogs will be tackled by a genome scan of before unknown comprehensibility with hopefully a resulting future gene test, and a breeding evaluation program which can be used by breeders after the publication is finished.
- The technological capabilities, the dually oriented goal approach, and the involved persons make it a state of the art scientific project. The fact that internationally renowned professors who have worked on epilepsy in Border Collies for decades, asked whether they could join in after we started, proves this fact.

Since all this work is going to cost a lot of money, we need funding. The ABCD as the German ISDS associated society will give a grant, and private persons also have donated.

If there are any further questions, do not hesitate to get in touch and ask. It is a rather complicated subject. I hope, I could describe the facts in a halfway understandable fashion.

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