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Genetics of Canine Epilepsy

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Abstract:

Epilepsy is the most common neurological disease in dogs and many forms are considered to have a genetic basis. Investigations of true canine epilepsies has revealed genetic associations in some cases, however many remain unexplained.

Gene mutations have been described for 2 forms of canine epilepsy, Primary (generalised) Epilepsy, which is the original diagnosed epilepsy itself and secondly Progressive Myoclonic Epilepsy, which are brief shock like jerks of a single muscle or muscle groups, during a myoclonic seizure the dog is usually awake.

Nine genes have been described to underlie progressive myoclonic epilepsies in several different dog breeds.

The investigations into Genetic Primary Epilepsy (PE) have been less successful, with only one causative gene described. Certain dog breeds and certain lines within in the breeds are predisposed to epilepsy including Australian Shepherds, German Shepherds, Beagles, Boxers, Border collies, Border terriers, Cavalier King Charles Spaniels and springer Spaniels.

Genetic testing is available and will help with diagnosis of specific epilepsy, the prognosis and also benefits breeders, as they will be able to identify carriers, therefore revise breeding plans to avoid future affected puppies. Many studies of dog breeds with primary Epilepsy have failed to identify specific genes or loci of interest. This suggests that inheritance is complex as it is in human genetic epilepsies. It may involve several genes and be reflective of environmental interactions.

What is Canine Epilepsy?

Epilepsy is a general term used for neurological disorders, a seizure caused by an abnormal electrical activity in the brain, that are characterised by involuntary muscle movement. The seizures may be due to a genetic predisposition or caused by trauma, toxins, a brain tumour, liver or kidney disfunction. Epilepsy can also be referred to as idiopathic, meaning there is no identifiable underlying cause.

Commonly the patient will have loss of consciousness or altered consciousness, usually tonic-clonic contractions.

Epilepsy is the condition where the patient has recurring seizures, from an intracranial cause. Seizures may be preceded by a period of unusual behaviour called the preictal phase, this may last minutes to hours.

Most seizures are followed by a postictal phase, during which the animal is disorientated and possibly ataxic or blind, this is called cortical blindness. Most seizures In dogs are generalised tonic-clonic seizures, where the animal first becomes stiff and then goes into repetitive muscle contractions and is usually followed by paddling of the feet.

In Generalised seizures the animal also loses consciousness. Animals can also have partial seizures, which can be localised to a specific part of the brain, based on presentation. For instance, psychomotor seizures arising from the limbic system, can cause transient behaviour changes such as sudden aggression, screaming, circling, or aimless running, fly-biting, tail chasing and

flank sucking can sometimes be attributed to partial seizures. (1)*Dr Sophia Yin*

Genetic Basis of Genetic Canine Idiopathic Epilepsy

Breeders and owners often ask what is known about the inheritance of idiopathic epilepsy. This is an important question because if breeders know the mode of inheritance (that is, the pattern of inheritance across generations), then they may be able to develop breeding strategies that will help them to breed away from epilepsy. Usually, if the mode of inheritance for a disorder is well understood, careful selective breeding can enable breeders to greatly reduce, or even eliminate, the disorder while allowing the breeders to continue with their bloodlines. Obviously, when some breeders and owners ask about the inheritance of epilepsy, they will be hoping they will not find that the seizures in their dogs are not due to inherited epilepsy. Sometimes, they do find reason to suggest this. However, many times, they must face the conclusion that inheritance (genetics) was the underlying cause of the seizures.

The purpose of this review is to see what is currently known about the mode of inheritance for canine idiopathic epilepsy. There are many causes of seizures in dogs (and humans) besides genetic epilepsy. These include, but are not limited to, head injuries, exposure to toxins, infectious diseases affecting the central nervous system, metabolic disorders, tumors and organ disfunction. Dogs should only be considered to have idiopathic epilepsy after these other causes of seizures have been ruled out by a very thorough work up of diagnostic tests.

Whilst discussing the inheritance of idiopathic epilepsy, the initial question that must be addressed is whether there is scientific evidence that idiopathic epilepsy is inherited. The answer to this question is "yes." There appear to be at least 25 breeds of dogs (some of which I have listed above) that show a significantly higher than average rate of idiopathic epilepsy. While suggestive, this alone does not indicate strong scientific evidence that idiopathic epilepsy is inherited. However, in addition to these statistics, a number of researchers have conducted pedigree analyses on particular breeds; and these analyses have found strong evidence that idiopathic epilepsy is inherited across generations.

A partial list of the breeds that show at least some evidence of a genetic predisposition to idiopathic epilepsy include: Beagles, Belgian Tervurens, Boxers, Cocker Spaniels, Collies, Dachshunds, Dalmatians, German Shepherds, Golden Retrievers, Irish Setters, Irish Wolfhounds, Labrador Retrievers, Pointers, Poodles (all varieties), Saint Bernards, Schnauzers (miniature, standard and giant), Siberian Huskies, Vizslas, Welsh Springer Spaniels, and Wire haired Fox Terriers.

Several breeds currently are being studied by different researchers to try to determine the specific mode of inheritance for idiopathic epilepsy (as well as to actually identify genetic markers that are linked to the genes that cause epilepsy). At the time of this article(February, 1999), however, no one has found any conclusive results. In addition, the mode of inheritance and/or the specific genes involved are likely to be different for different breeds. therefore, even when researchers make important discoveries for one breed, other breeds will need to be investigated separately to determine if the same conclusions apply.

The term "mode of inheritance," refers to whether the disorder is a simple recessive trait, a simple dominant trait, or a complex trait. Traits that are "simple" are carried by a single gene, while

traits that are complex involve more than one gene. With complex genetic traits, these different genes can combine or interact with each other, and the genes can also interact with the dog's environment.

Simple genetic traits seem to be easier to study. The "recessive" term means that a dog will only have the disorder if the defective gene is carried and passed by both of the parents. Therefore, if it is only one parent passing the defective gene, the offspring will not be affected with the disorder but they can be "carriers" and later pass their one defective gene to their own offspring. The term "dominant" means that the dog can have the disorder even if only one of the parents passes the defective gene.

As indicated, there currently are no conclusive findings on the mode of inheritance for canine idiopathic epilepsy. However, there are some general theories. Some investigators have theorized that, at least in the breeds they studied, the disorder is likely to be recessive because often two parents that are free of epilepsy produce offspring with epilepsy. Another theory concerns whether the defective gene or genes are carried on the sex chromosomes. (Each dog has 39 pairs of chromosomes which carry all of his or her genes. One member of each pair is inherited from each of the parents. Thirty-eight of these pairs are autosomes, meaning a chromosome which is not a sex chromosome and one pair is the sex chromosomes.) Often, when there are sex differences in a trait, the gene for that trait is carried on the sex chromosomes. However, despite the fact that many breeds (though not all) show a higher rate of epilepsy in males than females, the pattern of inheritance across generations suggests that the genes responsible for epilepsy are probably carried on one or more of the autosome pairs. While these two theoretical notions (recessive and autosomal) may indeed prove to be true for many breeds, at the present time, there still is not

enough data to draw any firm conclusions, even on the specific breeds for which pedigree analyses have been conducted.

As indicated, there are several researchers who currently are investigating the genetic basis of canine idiopathic epilepsy. If you own a dog with idiopathic epilepsy, or one of your dogs has produced offspring with epilepsy, please contact your breed's parent club to find out if any researchers are investigating your breed. If your breed's parent club is not sponsoring any research like this, encourage them to do so.

(2) Barbara Licht, Ph.D., Mark Licht, Ph.D., Kathy Harper, D.V.M, Ph.D., and Shili Lin, Ph.D. Canine Epilepsy Resorces

Candidate genes for idiopathic epilepsy in four dog breeds.

A Candidate gene (which is a gene or variation on a gene, that may relate to the construct of interest or in other words characteristics of individual interests given the role of that particular gene, in a distinct biological pathway or findings from previous studies)

Idiopathic epilepsy (IE) is a naturally occurring and significant seizure disorder affecting all dog breeds. Because dog breeds are genetically isolated populations, it is possible that IE is genetically homogenous within breeds. In humans, a number of mutations, the majority of which are genes encoding ion channels, neurotransmitters, or their regulatory subunits, have been discovered to cause rare, specific types of Idiopathic Epilepsy. It was hypothesized that there are simple genetic bases for

Idiopathic Epilepsy in some purebred dog breeds, specifically in Hungarian Vizslas, English Springer Spaniels, Greater Swiss Mountain Dogs and Beagles, and that the gene or genes responsible may, in some cases, be the same as those already discovered in humans.

THE RESULTS OF THIS STUDY SHOWED:

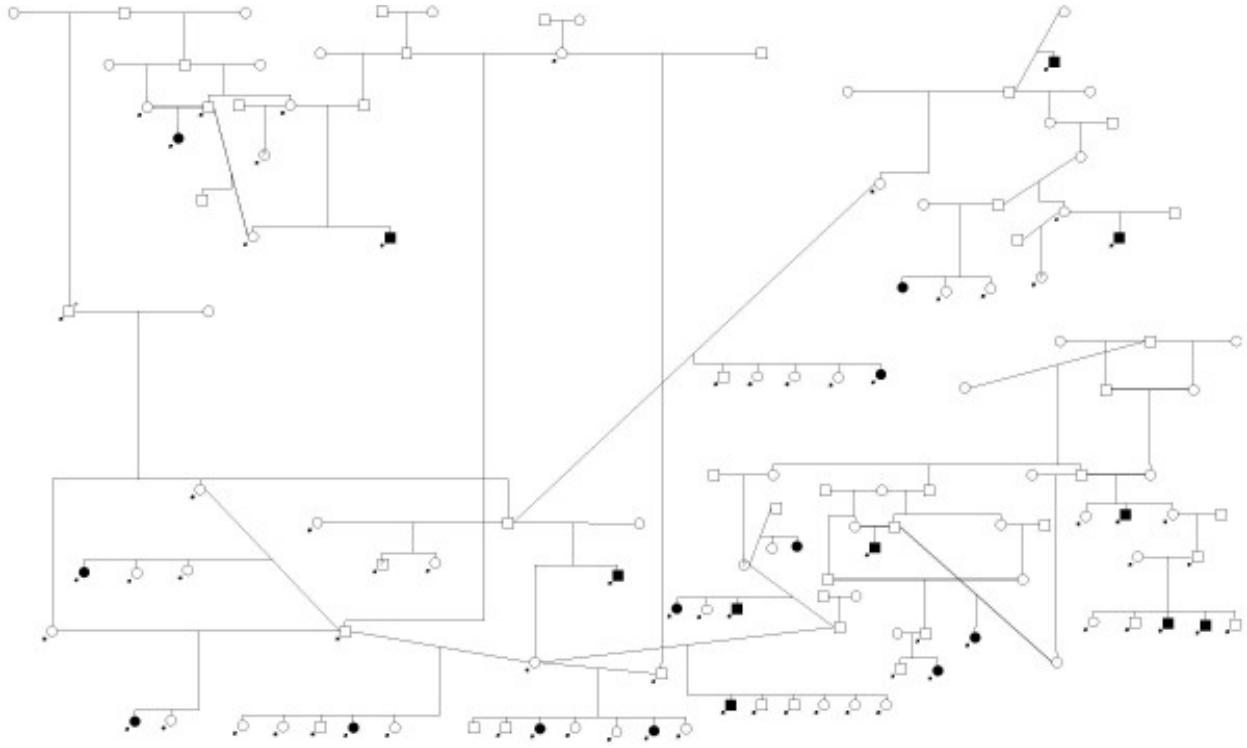
Candidate genes (which is a gene or variation on a gene, that may relate to the construct of interest, given the role of that particular gene, in a distinct biological pathway or findings from previous studies) known to be involved in human epilepsy, along with selected additional genes in the same gene families that are involved in murine epilepsy (mice or rodents) are expressed in neural tissue, were examined in populations of affected and unaffected dogs. Microsatellite markers (or single sequence repeats, which are widely used in DNA based genetic analysis) in close proximity to each candidate gene were genotyped and subjected to two-point linkage in Vizslas, and association analysis in English springer spaniels, Greater Swiss Mountain dogs and Beagles.

CONCLUSIONS:

Most of these candidate (characteristics of individual interest) genes were not significantly associated with Idiopathic Epilepsy in these four dog breeds, while a few genes remained inconclusive. Other genes not included in this study may still be causing monogenic (involving or controlled by a single gene) Idiopathic Epilepsy in these breeds or, like many cases of human Idiopathic Epilepsy, the disease in dogs may be polygenic (involving or controlled by 2 or more genes at different loci on different

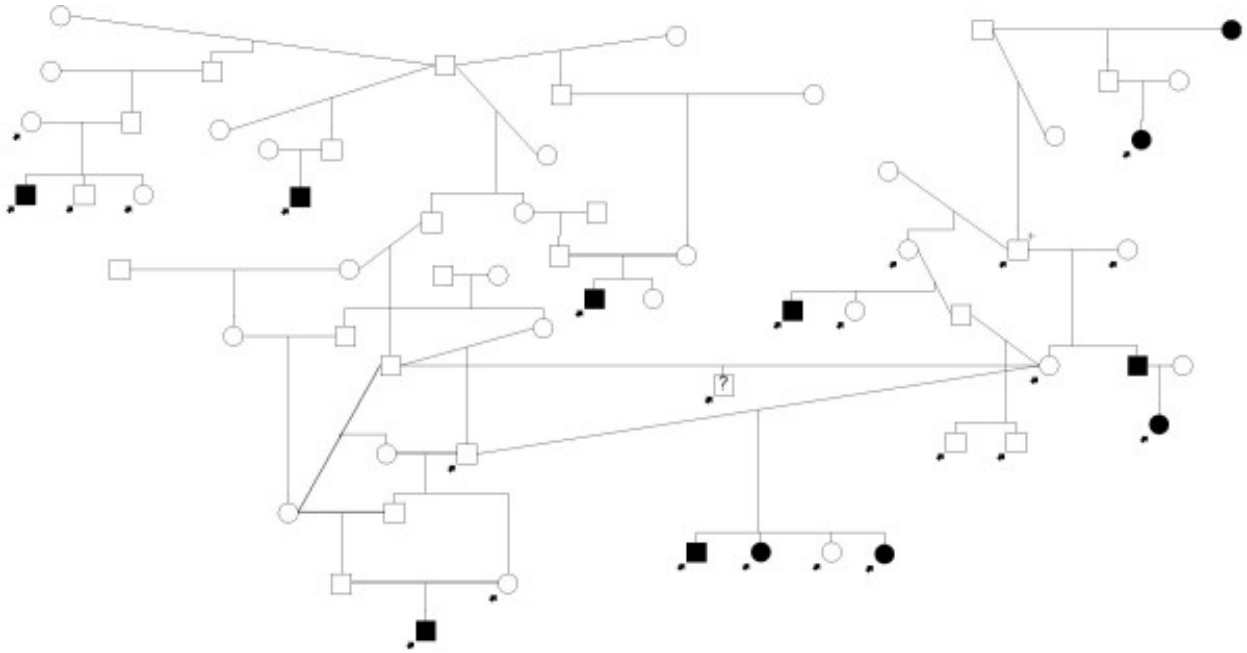
chromosomes, for example, height, hair colour, weight are determined by multiple genes)

Figure 1



Vizsla linkage family 1 pedigree. Pedigree of Vizsla family 1. Squares and circles represent males and females, respectively. Filled shapes represent cases; those with question marks represent unknown phenotype status. Dogs with arrows were genotyped in this study. The dog marked with an arrow and a + is included on both families 1 & 2, effectively making this one very large family. The Vizsla pedigrees were broken into ten smaller families to decrease inbreeding loops before being analysed in linkage analysis. Three dogs representing one of the ten sub-families are not shown on either pedigree.

Figure 2



Vizsla linkage family 2 pedigree. Pedigree of Vizsla family 2. Squares and circles represent males and females, respectively. Filled shapes represent cases; those with question marks represent unknown phenotype status. Dogs with arrows were genotyped in this study. The dog marked with an arrow and a + is included on both families 1 & 2, effectively making this one very large family. The Vizsla pedigrees were broken into ten smaller families to decrease inbreeding loops before being analysed in linkage analysis. Three dogs representing one of the ten sub-families are not shown on either pedigree.

Objectives to provide an appreciation for the complexity surrounding investigations of the genetic mechanisms underlying canine epilepsy:

Epilepsy affects all human populations at a rate of approximately 1%. Many other species also experience epilepsy including cats, horses, goats, cattle, non human primates, and rodents (Chandler, 2006). Epilepsy is especially common among dogs with an overall prevalence of 5% (Lohi et al., 2005). Some purebreds have a greater prevalence of repeated seizure activity, but all dog breeds, including non-purebred dogs, can have individuals with epilepsy. Given the general prevalence of epilepsy among domesticated canines and the relative higher prevalence within certain breeds, genetic contribution to the expression of epilepsy is expected. As an aside, epilepsy may be a consequence of domestication as wolves rarely exhibit seizures except under pharmacological treatment [personal communication, Dr. L. D. Mech, Senior Scientist with the Biological Resources Division, U.S. Geological Survey and an Adjunct Professor in the Department of Fisheries, Wildlife and Conservation Biology, and Ecology, Evolution and Behavior at the University of Minnesota].

Treatment of epilepsy is costly and often ineffective. Breeders are highly motivated to reduce the likelihood of producing puppies that will later be diagnosed with seizure episodes and have initiated studies to explore the genetic basis to the disorder. In addition, the epileptic seizures experienced by dog may offer insights into progression and potential therapeutics for the human condition. Sutter and Ostrander (2004) and Ellegren (2005) both emphasize the potential utility of dog breeds as models to dissect the genetics underlying complex human disorders. Thus, numerous investigators have been studying canine epilepsy at all levels: physiological, neurological, cellular, and molecular. Although the simplified genetic structure of certain dog breeds may be useful for understanding human disease, dog breeders want to reduce the prevalence of epilepsy in the dog. One of the first steps necessary to reduce the prevalence of epilepsy in a breed of dog is to characterize the genetic

contribution and predict the mode of inheritance of the condition.

Many investigators have evaluated breeds of dogs known for having a higher than expected prevalence of epilepsy. Based on assessment of pedigrees and phenotypic data, the published predicted canine models of epilepsy inheritance have been consistent with multilocus modes that include autosomal recessive with incomplete penetrance (Srenk et al., 1994; Famula et al., 1997; Jaggy et al., 1998; Patterson et al., 2005; Casal et al., 2006), although a single locus model has been proposed for idiopathic epilepsy in Keeshonds (Hall and Wallace, 1996) and Vizslas (Patterson et al., 2003).

Our laboratory has been investigating the inheritance of repeated seizures that appear to have no underlying cause, and represent generalized seizures (myoclonic, clonic, tonic clonic). An acknowledged limitation of our research population is that the condition is owner reported; usually by an owner whose dog experienced a seizure and, following a veterinary examination, learns about idiopathic epilepsy or by a breeder long familiar with the condition of idiopathic epilepsy. The subtle nuances of a seizure are often not detected nor reported and the diagnosis can never be definitive. This is a difficulty associated with seizure classification and therefore, the study of canine epilepsy (Chander, 2006). Nevertheless, owners of particular breeds are well aware of the condition and their reports are remarkably similar. For our study we restrict classifying dogs as epileptic to those that the owner describes as exhibiting generalized seizures. Licht et al. (2002) and Podell (2004) have recommended the application of the human International League Against Epilepsy (ILAE) seizure classification system to dogs that had experienced seizures. A more accurate description of canine seizures could refine epilepsy research and yield better treatment for dogs; a

consistent classification of seizures would improve the accuracy of heritability estimates and mode of inheritance predictions.

We have been accumulating generalized epileptic seizure data on Poodles (2116 dogs, 83 with repeated seizing activity), Giant Schnauzers (291 dogs, 25 with repeated seizing activity), English Mastiffs (630 dogs, 36 with repeated seizing activity), Belgian Sheepdogs (858 dogs, 117 with repeated seizing activity) and Belgian Tervuren (1064 dogs, 136 with repeated seizing activity). The prevalence of epilepsy among these admittedly biased samples ranges from ~4% to 13.6%. From the submissions we have organized dogs into familial structures to evaluate heritability. Figure 1 provides illustrations of portions of the pedigrees of submitted dogs. The expression of the seizing phenotype in the English Mastiff has an early profile of expression relative to other breeds. The average age of onset of the seizures in the English Mastiff is 29.2 months of age with 47% having their first seizure before 2 years of age and the oldest age for an English Mastiff to have begun seizuring is 57 months. That is in contrast to the Belgian Tervuren and Sheepdogs (where we have an abundance of data) where only 21% of the dogs have their first seizure prior to 2 years of age, Standard Poodles with a mean age of seizure onset of 42.7 months and 37.7% with their first seizure by 2 years of age, and Giant Schnauzers with an average age of onset of 36.2 months with 44% having their first seizure by 2 years of age. The very limited data for Toy and Miniature Poodles do not allow meaningful comparisons.

The heritability of seizures was estimated using a mixed model Bayesian analysis strategy in an ordered categorical threshold model. Narrow sense heritability was estimated with the SOLAR computational package using binary trait analysis. For heritability analyses, we have excluded young animals to preclude biasing the predictions. We wanted to avoid including dogs that may eventually seize but have not due to their young age. Therefore we

"censored" the data to exclude dogs under the age of four years unless those dogs were categorized as repeatedly seizing. We statistically assessed the heritability of epilepsy in the Standard Poodle (the Poodle variety with substantial submissions) and the estimate of heritability for seizures was 0.59 with a standard error of 0.28. The heritability was not significantly different for males vs. females. We have also estimated heritability of multiple seizures in the Giant Schnauzer even though the total number of submitted dogs is low; the number of dogs that have seized repeatedly was fairly high and the dogs with seizing activity were highly related which enabled the evaluation. For example, for one family we had six generations and 23 of the affected dogs. In the data set we evaluated 285 Giant Schnauzers with known health status, 25 of which seized repeatedly. The estimate of heritability was 0.78 and was highly significant ($p < 0.007$). Sex was not a significant contributor to the seizing phenotype. Using data on 588 English Mastiffs with known health status and parents with 33 of those recorded as seizing repeatedly, the estimate of heritability was 0.69 with a standard error of 0.44. The high standard error equates to a non significant estimate of heritability (the significance level is $p = 0.065$ and while nearly reaching the $p = 0.05$ for classical significance it is considered only tending toward significance). Of interest, though possibly reflecting low numbers of dogs in our analyses, males were more likely to be afflicted with repeated seizures than females ($p < 0.05$). We have published the data on the Tervuren and Sheepdogs and the estimate of heritability of epilepsy ranged from 0.77-0.83. Our work in Belgians suggest the predicted mode of inheritance is polygenic but with a single gene of large effect influencing expression of the epileptic phenotype.

In most instances the putative mode of inheritance of epilepsy in breeds that have been studied is "complex" or "polygenic". Yet most analyses also suggest an autosomal recessive major locus with the complexity being additional loci regulating penetrance.

As noted above, Ellegren (2005) considers the dog an extremely advantageous model for studying genetic disorders with a human counterpart: "each pure breed is an inbred, isolated genetic population with simplified genetic structures than can be linked to their physical traits." Sutter and Ostrander (2004) consider dog breeds to be ideal for unraveling disease alleles of complex disorders and cite the findings of quantitative loci associated with skeletal morphometrics in the Portuguese Water Dog.

While a dog model as whole is valuable for the identification of genes causing a disorder, caution must also be applied to prevent global generalization. Breeds are clearly distinct from one another although certain breeds do cluster together (Sutter & Ostrander, 2004). The importance of that fact lies in the basis for the distinctness: nucleotide heterozygosity and single nucleotide polymorphisms (SNP). Given the variability of the underlying DNA between breeds it is necessary to consider that dissimilar breeds may have different and distinct mutations that affect the expression of epilepsy. This is especially true given the nature of seizures and their inexact classification by dog owners and general practice veterinarians. This complicates the search for "the gene for epilepsy" that all breeders and dog owners desire.

However, Lohi et al (2005) identified a specific mutation associated with a rare form of epilepsy seen in miniature wirehaired dachshunds (MWHD). This research group noticed congruence between the seizure characteristics in the MWHD and a severe seizure disorder in humans, Lafora disease whose genetic mutation had been mapped. Taking advantage of the recent canine genome sequencing project and its synteny with the human genome, the investigators identified a mutation in the Epm2b gene (also known as NHRLC1) of affected MWHDs. This represented the identification of the first gene involved in any canine epilepsy, albeit a very restricted form. Perhaps most telling from this group's research is the number of different mutations

and genetic alterations identified within two genes, each of which results in the same epileptic phenotype of Lafora disease. This corroborates the hypothesis put forth by Licht et al. (2002) that different parental lines within a breed may manifest epilepsy through distinct genetic mechanisms. This last underscores the challenge faced by investigators searching for the genetic basis for canine epilepsy.

Nevertheless, the rapid advances in the canine genome with an increase in tools available for genetic searches should make it possible to identify alterations in the genome that underlie epilepsy. The now classical approach is to do a genome wide association study using microsatellite markers evenly spaced across the genome. In the Belgian Tervuren and Sheepdog, there has been a genome wide association study using microsatellite markers. In the population as a whole, particular alleles were more prevalent in dogs with seizures than in dogs that did not based on a linkage disequilibrium analysis. Then there was constructed extensive pedigrees and did haplotype analyses on the related dogs in which seizures segregate. A haplotype , meaning a set of genetic determinants located on a single chromosome.

In evaluating the haplotypes, there was no clear association between the haplotypes and the seizures across families although within one very small family, the haplotype transmission appeared strong. The absence of haplotype linkage may reflect phenocopy; overall certain families exhibit seizure characteristics similar to other families and the genetics similarly reflect the influence of a single autosomal recessive gene, the actual gene that is altered may differ between families as has been suggested by Licht et al., (2002). That is, while as a whole, the population of Tervuren and Sheepdogs exhibit a major gene inherited as an autosomal recessive, the precise mutation or gene may differ in different families even though generating a remarkably similar phenotype. This study has now focused its attention on small,

single families rather than on the broader more extensive family; that is looking at the subset families within the larger family that was assembled.

Based on the indication of a significant genetic contribution to the expression of seizures as indicated by the high heritability estimates in the other breeds, they initiated a search for genetic linkage between the seizing phenotype and a particular chromosomal region. They approached this by doing a homozygosity analysis in which 8 highly unrelated dogs are screened using the minimal screening set II of 327 microsatellite markers (MSS-2, offering 9 Mb coverage) markers. This approach presumes an autosomal recessive mode of inheritance and that the unrelated individuals only share the DNA that encodes (or is linked to) the region causing the mutation responsible for the seizuring phenotype. They selected 8 unrelated English Mastiffs and 8 unrelated Standard Poodles.

For the English Mastiffs, the chromosomes showing some association were 1, 2, 5, 7, 8, 9, 10, 11, 18, 23, 26, 27, 30, 31, 32, 33, and 34. The high number of chromosomes exhibiting homozygosity (possession of two identical alleles of a particular gene by an individual) may reflect that the breed is more homozygous as a whole and that the homozygosity approach will not offer any improvement over a generalized genome scan to identify linkage.

In the Standard Poodles, the chromosomes showing some association were 1, 3, 5, 12, 23, and 32. It was found to be interesting that both the Standard Poodle and the English Mastiff demonstrated homozygosity on chromosomes 1, 5, 23, and 32. This approach utilizes the linkage disequilibrium or loss of stability that exists within dog breeds. The genetic material surrounding a mutation should be ancestral and held in common

among dogs that carry the altered DNA. However, certain dog breeds may have experienced severe bottlenecks and the linkage disequilibrium may be extensive rendering the classical approach less effective meaning more and more variable markers must be used. The newly available SNP chip (single nucleotide polymorphism) offers the best approach to mapping complex disease traits. It is a DNA microarray which is used to detect polymorphisms within a population.

In summary

The complex nature of canine epilepsy will prove challenging with respect to determining the underlying genetic mechanisms responsible. However, the advancements in the DNA technologies will enable scientists to unravel regions of the chromosome regulating this debilitating disorder.

Treatment of canine epilepsy:

Affilations here to: The Department of clinical science and services, Royal Veterinary college, Hawkshead London. Marios Charalambous and Holger A Volk.

Various antiepileptic drugs are used for the management of canine idiopathic epilepsy. Information on their clinical efficacy remains limited.
A systematic review was designed to evaluate existing evidence for the effectiveness of Anti-epileptic drugs for presumptive canine idiopathic epilepsy. Electronic searches of PubMed bio-medical literature and CAB Direct abstracts archive database platform, a source of reference in the applied life sciences (It incorporated two bibliographic databases CAB abstracts and global health) were carried out without date or language restrictions. Conference proceedings were also searched. Peer-reviewed full-length studies describing objectively the efficacy of AEDs in dogs with IE were included. Studies were allocated in two groups, blinded randomised clinical trials, non-blinded randomized clinical trials and non-randomized clinical trials (group A) and uncontrolled clinical trials and case series (group B). Individual studies were evaluated based on the quality of evidence (study design, study group sizes, subject enrolment quality and overall risk of bias) and the outcome measures reported (in particular the proportion of dogs with ≥50% reduction in seizure frequency).

The results were as follows:

Twenty-six studies, including two conference proceedings, reporting clinical outcomes of anti-epileptic drugs used for management of Idiopathic epilepsy were identified. Heterogeneity

of study designs and outcome measures made meta-analysis inappropriate. Only four blinded randomised clinical trials were identified in group A and were considered to offer higher quality of evidence among the studies. A good level of evidence supported the efficacy of oral phenobarbital and imepitoin and fair level of evidence supported the efficacy of oral potassium bromide and levetiracetam. For the remaining Anti-epileptic drugs, favourable results were reported regarding their efficacy, but there was insufficient evidence to support their use due to lack of blinded randomised clinical trials.

Conclusions on treatments of canine Epilepsy

Oral phenobarbital and imepitoin in particular, as well as potassium bromide and levetiracetam are likely to be effective for the treatment of Idiopathic Epilepsy. However, variations in baseline characteristics of the dogs involved, significant differences between study designs and several potential sources of favouritism prevent definitive recommendations. There is a need for greater numbers of adequately sized Blind Randomised clinical trials evaluating the efficacy of Anti-Epileptic drugs for Idiopathic Epilepsy.

Final conclusions on my literature review

I asked myself is Epilepsy the same in all dog breeds?

No it is not. There have been over 15 genes defined so far which cause epilepsy in humans and a similar number in mice, and it is likely that many additional epilepsy-causing genes will be found in the future. This same assortment of genes however may be responsible for epilepsy in dogs. Within some breeds, all the dogs with epilepsy appear to follow the same basic pattern.

In other breeds there may be several different patterns, or no apparent pattern at all. It is possible that each breed and each different pattern has a different genetic mutation. It is also possible that several breeds who all follow the same pattern may all have the same or very similar mutations. Research is only just beginning to search for these answers.

What are DNA researchers actually looking for in their studies?

DNA researchers attempt to find the genes responsible for various traits, both detrimental and beneficial. Like the human genome and mouse genome project, the canine genome project is trying to determine how the genes are arranged on the various chromosomes and what they actually do. While good progress has been made mapping the human and mouse genome, the canine gene map until recently has been pretty rudimentary, which makes genetic research much slower and more challenging. The goals of DNA researchers working on canine epilepsy are:

(1) To identify the gene or genes responsible for the various forms of canine epilepsy;

(2) To characterize the responsible mutations within the epilepsy genes;

(3) To come up with and approve DNA marker assays or checks, that can detect the epilepsy causing mutations. These DNA marker assays should facilitate breeders to produce epilepsy free puppies.

Will a DNA testing be conclusive for all dogs within a breed?

Each epilepsy causing mutation stems from a particular mutation event that has occurred in a specific ancestor. If several mutation

events are contributing to the epilepsy in a breed it will take several DNA tests to completely eliminate epilepsy from the breed. However it is likely that one or a few mutations are responsible for most of the epilepsy in a particular breed so one or a few tests would go a long way toward eliminating epilepsy in these breeds.

Although several research groups are looking for epilepsy genes in a variety of dog breeds, we are not aware of any successes as of yet to finding “an Epilepsy gene”. Predicting how long it will take to find the mutation or mutations and develop a test is frustrating, it’s like one step forward and two steps back.

Primary testing work does look encouraging, but more research needs to be done, and more families are needed for testing. I do believe that with time and access to revealing families, markers will be identified in many dog breeds.

In my research I spoke to a breeder of miniature poodles, she has all her dogs DNA tested and even purchased puppies from a breeder in Budapest due to excellent ancestral traits. She shows and breeds her dogs.

If epilepsy is a recessive trait or a polygenic (2 or more genes) trait, then carriers can be bred to DNA-tested normal dogs without producing offspring that will develop clinical signs of epilepsy.

However, such a breeding will produce some puppies who are clear, and some who are carriers. Therefore, it is essential that the offspring from such a breeding also be DNA tested before they are bred. The key is to know the genetic status of BOTH dogs involved in any breeding. Selection of a carrier in a breeding programme should be done very carefully and the breeder ethically must share this information with the buyers of the puppies.

The tests can be done on DNA from a dog of any age. Docked tails (in breeds where this is customary) are a good source of DNA if the breeder can keep track of which pup goes with which tail, this is more so in the US as tail docking is illegal in Ireland.

Blood samples are difficult to draw from young puppies , vets would recommend you wait until the pups are over 7 weeks of age to collect a blood sample for testing.

Finally a brief mention on the current evidence behind epilepsy surgery in veterinary medicine.

Epilepsy in dogs has been found to be the most common chronic neurological disorder, with a reported prevalence of 0.5% - 5% in non referral populations (Ekenstedt and Oberbauer, 2013, Podell et al., 1995).

In UK, this prevalence was estimated to be 0.62% (Kearsley-Fleet et al., 2013). Drug-resistant canine epilepsy has been previously reported to affect as high as 30% of all dogs with idiopathic epilepsy (Lane and Bunch, 1990). Despite the fact that drug-resistant epilepsy can commonly occur in dogs, there is no or limited evidence behind surgical treatment options.

There is one report in which experimental corpus callosotomy (surgical division of corpus callosum, a wide, thick nerve tract, consisting of a bundle of fibres, beneath the cerebral cortex in the brain) in a very small number dogs with drug-resistant epilepsy was performed and showed encouraging initial short-term results (Bagley et al., 1996). However, the long-term outcome in these canine patients was not evaluated and further details related to the study design were not widely accessible. Due to this fact and the several limitations of the study, the overall risk of bias might

be considered high. Therefore, surgical epilepsy has been inadequately described in dogs.

The reason is mainly due to the fact that the Epileptogenic zone and or the Irritative zone have not been extensively defined or described in animals and the lack of application of advanced functional neuroimaging techniques (e.g., EEG, electroencephalogram MEG, magnetoencephalography, fMRI, functional magnetic resonance imaging). The fMRI is highly important in order to map and successfully localise the epileptogenic area. EEG has been used though in veterinary medicine to detect abnormal discharges in various diseases in dogs (Chandler, 2006) as well as interictal spikes in epileptic anaesthetized dogs (Jaggy and Bernardini, 1998, Srenk and Jaggy, 1996).

The introduction of EEG in veterinary medicine as a routine diagnostic technique in the near future might change the current state and possibly form the base of epilepsy surgery in animals.

Acknowledgments

Foremost I would like to thank my supervisor *Prof. Zöldág László* for allowing me to choose this thesis as my topic, and also for his direction, support and enthusiasm while writing my thesis.

I would also like to extend many thanks to the University of Veterinary Medicine Budapest, especially the department of Animal Breeding and Genetics, who provided me with the facilities to undertake this study.

I am profoundly grateful to all my family, friends and future Veterinary colleagues for their encouragement and support during the research and writing of my thesis.

I have yet to meet them but Dr Marios Charalambous and Professor Volk Holger at The Department of clinical science and services, Royal Veterinary college, Hawkshead London.
have always been available to answer my emails about their research and hopefully I will get to meet them soon.

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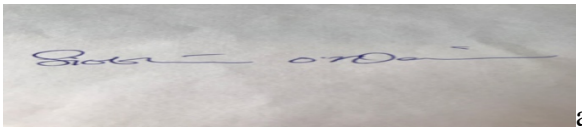

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