Topical Review

Inherited Epilepsy in Dogs

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Epilepsy is the most common neurologic disease in dogs and many forms are considered to have a genetic basis. In contrast, some seizure disorders are also heritable, but are not technically defined as epilepsy. Investigation of true canine epilepsies has uncovered genetic associations in some cases, however, many remain unexplained. Gene mutations have been described for 2 forms of canine epilepsy: primary epilepsy (PE) and progressive myoclonic epilepsies. To date, 9 genes have been described to underlie progressive myoclonic epilepsies in several dog breeds. Investigations into genetic PE have been less successful, with only 1 causative gene described. Genetic testing as an aid to diagnosis, prognosis, and breeding decisions is available for these 10 forms. Additional studies utilizing genome-wide tools have identified PE loci of interest; however, specific genetic tests are not yet developed. Many studies of dog breeds with PE have failed to identify genes or loci of interest, suggesting that, similar to what is seen in many human genetic epilepsies, inheritance is likely complex, involving several or many genes, and reflective of environmental interactions. An individual dog's response to therapeutic intervention for epilepsy may also be genetically complex. Although the field of inherited epilepsy has faced challenges, particularly with PE, newer technologies contribute to further advances.

Introduction

Epilepsy is the most common chronic neurologic disorder in dogs, reported at a prevalence of between 0.5% and 5% in a nonreferral population,[1] and humans, where it is estimated to affect 1%-3% of the population.[2] However, epilepsy is not a single disease but a group of disorders characterized by a broad array of clinical signs, age of onset, and underlying causes. The International League Against Epilepsy classifies human epilepsies and defines terminology for the various etiologies; these terminologies are as follows: (1) genetic (or primary), (2) structural/metabolic (including symptomatic), and (3) unknown, in which the mechanistic basis is not yet elucidated.[3] The proposed canine classification for epilepsy is a slight modification of that by the International League Against Epilepsy: (1) primary/genetic epilepsy (often termed "idiopathic" epilepsy), (2) structural epilepsy (symptomatic epilepsies resulting from structural brain abnormalities), (3) reactive seizures (symptomatic epilepsies resulting from metabolic or toxic abnormalities), and (4) unknown. Some epilepsies bridge these categories; for example, genetic mutations may be the cause of a metabolic abnormality that results in epilepsy. Owing to clinical presentation, these epilepsies are still classified as metabolic, despite the genetic cause of their disorder. When chronic, recurring seizures occur and no underlying abnormality is detected, the syndrome is classified typically as primary epilepsy (PE) and presumed to be genetically regulated. Indeed, in humans, primary (or idiopathic) epilepsy is generally accepted to have an underlying genetic origin.[4]

Genetic epilepsies have been studied extensively in humans and mice, and, although an in-depth review of these species has not been undertaken in this article, it is worth noting that many parallels exist between syndromes in humans, mice, and dogs. In humans, genes underlying several rare, monogenic mendelian genetic epilepsies have been identified. Many are categorized as "ion channelopathies," with mutations in genes encoding sodium, calcium, potassium, and chloride ion channels. Causal mutations have also been observed in other genes involved in neuronal signaling, including neurotransmitter receptor genes, such as gamma-aminobutyric acid receptors or acetylcholine receptors. A small number of non–ion channel genes, previously unknown to be involved in the neural system, have also been implicated. Additional details on these known human genetic epilepsy mutations can be found in reviews.[4-10] Despite these discoveries, most of the human genetic epilepsies remain unsolved at the molecular level, and although most appear to have a strong genetic basis, their inheritance patterns are complex, with many contributing genetic and environmental factors. Greater than 95% of human non-mendelian epilepsies appear to be complexly inherited.[11] Genome-wide investigations have failed to uncover major regulatory loci suggesting that the underlying cause includes both rare and common allele variants each contributing small effects that may confer risk or protection for epilepsy.[12] Great interest exists to identify casual mutations to reduce the risk of epilepsy or inform and improve therapies.

Dozens of epileptic mouse models exist, each representing different causative mutations. A few represent spontaneous mutations, though most have been engineered intentionally.[13,14] As is the case for humans, many of these are ion channels genes, although non–ion channel genes can also underlie single gene murine epilepsy. For complexly inherited epilepsy, the epilepsy-like mouse strain suffers seizures in response to physical stimuli, such as moving a mouse from one cage to another.[15] The epilepsy-like mouse exhibits a polygenic complex phenotype and has at

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Table 1
Seizure Characteristic in Breeds With Clinical Descriptions of Potentially Inherited Primary Epilepsy

Breed*	Seizure Characteristics	Age of Onset	Genetic Basis	Sex Influence	References
Australian shepherd	Generalized, some with focal onset, some with secondary generalization	Under 5 y	Hereditary basis	Bias toward males	30
Beagle	Partial and generalized	1 y minimum	Significant sire effect	Bias toward males	31
Belgian Shepherd	Most focal onset, some with secondary generalization	Mean of 3.3 y	Simple mendelian, likely autosomal	No bias	26
Belgian Shepherd	Generalized	Mean of 4 y	Polygenic	No bias	32
Belgian Tervueren	Not reported	Widely variable	Hereditary basis, single-locus models not adequate to explain	No bias	33
Belgian Tervueren	Not reported	Not reported	Suspected single locus of large effect, with complex pattern of inheritance	No bias	34
Belgian Tervueren and Sheepdog	Generalized	Not reported	Polygenic	No bias	35
Bernese Mountain Dog	Most generalized	1-3 y	Polygenic autosomal recessive, sex modified	Bias toward males	36
Border Collie	Generalized, many with initial focal onset	Under 5 y	Autosomal recessive or more complex and resembling recessive	No bias	37
Dalmatian	Most partial onset with secondary generalization	3 y	Not determined	Slight bias toward females	38
English Springer Spaniel	Partial and generalized	Under 6 y	Partially penetrant autosomal recessive or polygenic	No bias	39
German Shepherd Dog (British Alsatian)	Not reported	1-2 y	Sire effect and affected dogs more inbred	Bias toward males	40
Golden Retriever	Most generalized	1-3 y	Polygenic autosomal recessive	Bias toward males	41
Irish Wolfhound	Generalized	Under 3 y	Incompletely penetrant recessive, with sex predilection	Bias toward males	42
Keeshond	Not reported	1 y minimum	Hereditary basis	Bias toward males	43
Keeshond	Not reported	Not reported	Suspected single autosomal recessive	No bias	44
Labrador Retriever	Most generalized with possible partial onset	1-3 y	Polygenic autosomal recessive	No bias	45
Labrador Retriever	Partial and generalized	Under 4 y	Not determined	No bias	46
Lagotto Romagnolo	Varies, with some simple focal and others complex focal or secondarily generalized	5-9 wks, remitting by 4 mo of age	Autosomal recessive, with possible incomplete penetrance and ~7% diseased with heterozygosity	No bias	24
Petit Basset Griffon Vendeen	Most focal onset, some with secondary generalization	Mean of 2.2 y	Likely hereditary basis owing to clustering within litters	No bias	47
Schipperke	Partial and generalized	Mean of 4.4 y	Not determined	Not reported	48
Standard Poodle	Most partial onset with secondary generalization	3 y	Not determined	No bias	38
Standard Poodle	Most partial onset, with occasional secondary generalization	Under 7.5 y	Simple autosomal recessive, with complete or nearly complete penetrance	No bias	49
Vizsla	Partial and generalized	1-3 y	Autosomal recessive, possibly polygenic	No bias	50

* Breeds listed are those described in the literature possessing a clinical picture consistent with PE. The most specific speculated or known mode of inheritance provided by the reference publication is provided

Lafora disease in the miniature wirehaired Dachshund.[56] This autosomal recessive disease is the result of a biallelic expansion of a dodecamer repeat in the *EPM2B* gene. Lafora disease is also observed in humans and mutations have been described in the laforin (*EPM2A*) gene[66] and the malin gene, (*NHLRC1*, also called *EPM2B*),[67,68] the latter being orthologous to the gene mutated in miniature wirehaired Dachshunds. Lafora disease is characterized by histopathologic changes consisting of intracellular Lafora bodies in multiple tissues, including brain, muscle, liver, and heart.[68,69] This is a clear demonstration of mutations in the same gene creating similar disease in different species. In another breed, a case report described Lafora disease in a single Beagle, although the presence of the expansion mutation was not assessed.[70]

Most successful have been the investigations of neuronal ceroid-lipofuscinoses (NCLs) for which 8 genes have been identified, all with autosomal recessive inheritance (summarized in

markers dispersed throughout the entire genome. Finally, GWA studies use the dense, inherent variability (single nucleotide polymorphisms [SNPs]) in the genome to compare the DNA of cases and controls. The alleles defined by the SNPs or the genetic markers are used to determine whether 1 allele occurs more often in cases than in controls, thereby indicating the genetic region associated with that allele is involved in disease expression.

One candidate gene study focused on genes already known to be involved in human or murine genetic epilepsy.[74] The hypothesis for the study was that a founder effect in the breeds would enable linkage or association detection. Fifty-two genes, predominantly for ion channels and neurotransmitter receptors, were evaluated in Beagle, Greater Swiss Mountain Dog, English Springer Spaniel, and Vizsla families. Despite the number of genes and dogs assessed, no major associations or linkages to PE were uncovered in any of the breeds and the plausible candidate genes were essentially ruled out.

Although the Collie breed is not reported to have a high prevalence of inherited PE, the well-known mutation in the *ABCB1* gene (also known as the *MDR1* or multidrug resistance 1 gene, originally described in Collies sensitive to ivermectin[75]) was recently investigated for an association with epilepsy in that breed.[76] Of the 29 Collies with PE, 48% were homozygous for the *ABCB1* mutation, 38% were heterozygous for the mutation, and only 14% were homozygous for the wild-type allele. Interestingly, those homozygous for the mutation had significantly improved seizure outcome (defined as having ≤1 seizure per month and no cluster seizures while being maintained on at least 1 antiepileptic drug [AED]) compared with the heterozygous dogs or dogs that were homozygous for the wild-type allele. A similar study of Australian shepherds[30] examined the *ABCB1* mutation in 50 PE cases and 50 controls and found that 22% of the cases and 18% of the controls were heterozygous for the *ABCB1* mutation, whereas 2% of both groups were homozygous for the mutation, indicating no significant association between the mutation and PE. Further, the *ABCB1* genotype was unrelated to the age at the onset of seizures, clinical course, remission, or seizure control with AEDs in the Australian shepherd. The significance of these genotypic findings as an aid in epilepsy prognosis, though intriguing, remains uncertain; further investigations with additional Collies and Australian shepherds, and inclusion of other breeds with the *ABCB1* mutation such as the Border Collie, are warranted.

Another candidate gene study examined a previously published 38-base pair variable number tandem repeat (VNTR) in the dopamine transporter gene in epileptic Belgian Malinois.[77] The VNTR is either present as a single copy or as 2 copies, with the single copy being less common within the breed. Though the number of PE-affected Belgian Malinois was small ($n = 5$), all were homozygous for the single copy. In addition, Belgian Malinois with at least 1 copy of the single VNTR had an increased frequency of loss of responsiveness to environmental stimuli (such as the dogs' eyes "glazing over"), which could be a clinical manifestation of a focal seizure or an absence seizure. These findings are preliminary and must be replicated in a large cohort of dogs. The fact that a few dogs that were homozygous for the single dopamine transporter VNTR did not have seizures implies that this type of epilepsy in Belgian Malinois is likely caused by more than 1 gene; indeed, a GWA study (described later) has identified a second associated chromosomal locus.

The advent of high-density SNP arrays used in GWA studies are valuable for complex trait assessment, although those conducted for PE using the newer arrays in multiple breeds have met with mixed success, underscoring once again the multifactorial nature of the disease. Early linkage studies identified tentative loci associations to several genomic regions associated with PE in the Belgian Shepherd.[32] One of the loci identified was corroborated by results obtained from a GWA study that identified in Belgian Shepherd dogs a novel PE locus on Canis familiaris chromosome (CFA) 37 (canine chromosome 37); the locus was confirmed in a replication cohort.[78] A highly associated nonsynonymous CFA37 variant was identified in the *ADAM23* gene, and homozygosity for 2 separate SNPs within this gene resulted in a high risk for epilepsy. The gene product of *ADAM23* interacts with proteins LGI1 and LGI2, the latter of which has already been associated with PE in Lagotto Romagnolos (described earlier). This locus may also be associated with epilepsy in the Kromfohrländer and the Whippet, although these breeds require confirmation in a larger cohort. The variant, however, is not pathogenic based on predicted changes to protein structure, therefore, this is not a causative mutation. Further work, including targeted resequencing of the locus, is being undertaken.

Other GWA studies of PE have identified suggestive loci. For example, in Schipperkes, 2 loci were identified on CFA 26 and 31, which were tentatively associated with PE.[48] The Australian shepherd has likewise been studied in a GWA study, and associations were initially found to CFA19 (genome-wide significant) and CFA1 (slightly less significant).[79] Replication cohorts ultimately could not confirm the CFA19 association, but did improve the CFA1 locus' significance slightly. Combined with the *ABCB1* data mentioned earlier, these results suggest that PE in Australian shepherds is genetically complex, with several loci involved in the etiology. Other GWA studies have mapped PE loci to several different chromosomes for various breeds, but specific mutations have not yet been described.[80]

Unfortunately, many GWA studies investigating canine PE remain unpublished because results failed to achieve genome-wide significance and do not identify any associated loci. This is true for earlier genome-wide linkage studies and candidate gene studies as well. Studies using fewer markers may have failed to detect PE loci or all involved loci owing to lack of depth of coverage. The fact that newer, high-density SNP arrays used in recent studies also fail to uncover significant associations suggests that many canine PEs are oligogenic or polygenic, not unlike what has been observed in human PEs.

Pharmacogenetic Investigations of Canine PE

Parallel with the search for disease-causing epilepsy mutations, studies have been undertaken to investigate the genetic response to drugs and AED resistance in PE cases. For example, the *ABCB1* gene (described earlier) has been examined in Border Collies with PE. Affected Border Collies are often poorly controlled with AEDs, and resistance develops in up to 71% of cases.[37] A recent study determined that a sequence variation in the *ABCB1* promoter region (not the ivermectin sensitivity mutation found in exon 4) was associated with drug responsiveness in this breed[81]; this may indicate that expression of this gene could influence a dog's reaction to AEDs. Another study examined Australian shepherds with PE for the actual ivermectin sensitivity mutation (*ABCB1* genotype) and seizure control, but they did not establish an association.[30] Finally, a study examining the *ABCB1* genotype in Collies exhibiting PE observed that dogs homozygous for the *ABCB1* mutation received a reduced AED regimen than did the other 2 genotypes[76]; specifically, the dogs homozygous for the mutation, 93%, were given 1 AED, whereas the remaining 7% received 2 AEDs; the dogs that were heterozygous for the mutation or homozygous normal, were on 1 AED (40%), 2 AEDs (53%), or 3 AEDs (1 dog). Doses of phenobarbital did not differ significantly between genotypes; however, for those dogs receiving bromide, the dose was significantly lower in dogs homozygous for the mutation compared with the other 2 genotypes. Similar

abnormalities. Practitioners can advocate for improved definition of canine epileptic syndromes, and research directed at unifying the diagnostic criteria would aid genetic researchers. Although it is impractical for most canine PE patients to undergo EEG evaluation, perhaps there exist metabolic markers that reflect a particular EEG profile that could improve classification of the PE condition. Similarly, it would be ideal for dogs classified as unaffected to undergo EEG to verify normality before being included in genetic studies as controls. One recent review[71] points out that there has been a tendency to include reactive seizures in "case" groups of dogs with PE, which may falsely inflate prevalence rates, and would certainly affect the success of genetic investigations. For example, Arrol et al.[104] recently examined 136 dogs whose first seizure occurred before 1 year of age. Ultimately, 75% were diagnosed with PE, while 17% were diagnosed with symptomatic epilepsy, 7% with reactive, nonepileptic seizures, and 2 dogs were considered probable symptomatic. This underscores the need for specialized veterinarian diagnosis to prevent bias in classifying a dog as having PE in juvenile-onset canine seizures.

Because inherited canine seizure disorders exist that cannot be described as true epilepsy, it is essential for the practitioner to consider the breed presenting with seizures and the patient's clinical signs to discern how the seizure or seizurelike disorder should be treated. This would guide decision making as to whether or not genetic testing is appropriate, if the patient should be treated with AEDs, or if other, or any, therapies will favorably alter the course of disease.

The slow progress in identifying canine PE genes suggests that, just as in humans and some mouse models, epilepsy may present a much more complex genetic picture than originally hypothesized. The data to date indicate that the genetic risk for epilepsy is complex, including interaction between multiple genes and environmental factors. Variants may contribute small effects, and likely include both susceptibility and protective alleles. Canine studies would move in the same direction as human studies, that is, undertaking whole-genome sequencing of individual dogs, combining CNV studies with existing GWA studies, and pursuing epigenetic investigations. Though the remaining questions are formidable, studies of genetic inherited epilepsy have not been without reward. Ten gene tests are now available, and much work is still in progress. The promise of identifying chromosomal loci and genes involved in canine epilepsies brings hope for additional susceptibility tests for dog breeders, increasing our knowledge of the pathophysiology of neuronal hyperexcitation, and, possibly, development of novel pharmaceutical or gene therapies or both.

References

1. Podell M, Fenner WR, Powers JD. Seizure classification in dogs from a nonreferral-based population. *J Am Vet Med Assoc* **206**:1721–1728, 1995
2. Engel Jr. J. Intractable epilepsy: definition and neurobiology. *Epilepsia* **42** (Suppl. 6):3, 2001
3. Berg AT, Berkovic SF, Brodie MJ, et al. Revised terminology and concepts for organization of seizures and epilepsies: report of the ILAE commission on classification and terminology, 2005-2009. *Epilepsia* **51**:676–685, 2010
4. Gardiner M. Genetics of idiopathic generalized epilepsies. *Epilepsia* **46**(Suppl. 9): 15–20, 2005
5. Gurnett CA, Hedera P. New ideas in epilepsy genetics: novel epilepsy genes, copy number alterations, and gene regulation. *Arch Neurol* **64**:324–328, 2007
6. Poduri A, Lowenstein D. Epilepsy genetics-past, present, and future. *Curr Opin Genet Dev* **21**:325–332, 2011
7. Turnbull J, Lohi H, Kearney JA, et al. Sacred disease secrets revealed: the genetics of human epilepsy. *Hum Mol Genet* **14**:2491–2500, 2005
8. Greenberg DA, Pal DK. The state of the art in the genetic analysis of the epilepsies. *Curr Neurol Neurosci Rep* **7**:320–328, 2007
9. Baulac S, Baulac M. Advances on the genetics of mendelian idiopathic epilepsies. *Neurol Clin* **27**:1041–1061, 2009
10. Gallentine WB, Mikati MA. Genetic generalized epilepsies. *J Clin Neurophysiol* **29**:408–419, 2012
11. Petrovski S, Kwan P. Unraveling the genetics of common epilepsies: approaches, platforms, and caveats. *Epilepsy Behav* **26**:229–233, 2013
12. Kearney JA. Advances in epilepsy genetics and genomics. *Epilepsy Curr* **12**:143–146, 2012
13. McNamara JO, Puranam RS. Epilepsy genetics: an abundance of riches for biologists. *Curr Biol* **8**:R168–R170, 1998
14. Meisler MH, Kearney J, Ottman R, Escayg A. Identification of epilepsy genes in human and mouse. *Annu Rev Genet* **35**:567–588, 2001
15. Frankel WN. Detecting genes in new and old mouse models for epilepsy: a prospectus through the magnifying glass. *Epilepsy Res* **36**:97–110, 1999
16. Flavin HJ, Seyfried TN. Enhanced aspartate release related to epilepsy in (EL) mice. *J Neurochem* **63**:592–595, 1994
17. Frankel WN, Valenzuela A, Lutz CM, Johnson EW, Dietrich WF, Coffin JM. New seizure frequency QTL and the complex genetics of epilepsy in EL mice. *Mamm Genome* **6**:830–838, 1995
18. Frankel WN, Johnson EW, Lutz CM. Congenic strains reveal effects of the epilepsy quantitative trait locus, El2, separate from other el loci. *Mamm Genome* **6**:839–843, 1995
19. Rise ML, Frankel WN, Coffin JM, Seyfried TN. Genes for epilepsy mapped in the mouse. *Science* **253**:669–673, 1991
20. Shearin AL, Ostrander EA. Leading the way: canine models of genomics and disease. *Dis Model Mech* **3**:27–34, 2010
21. Ostrander EA, Kruglyak L. Unleashing the canine genome. *Genome Res* **10**:1271–1274, 2000
22. Lindblad-Toh K, Wade CM, Mikkelsen TS, et al. Genome sequence, comparative analysis and haplotype structure of the domestic dog. *Nature* **438**:803–819, 2005
23. Lorenz MD, Coates JR, Kent M. *Handbook of Veterinary Neurology*. 5th ed. 2011 St. Louis: Elsevier/Saunders; 2011. p.
24. Jokinen TS, Metsahonkala L, Bergamasco L, et al. Benign familial juvenile epilepsy in lagotto romagnolo dogs. *J Vet Intern Med* **21**:464–471, 2007
25. Berendt M, Gullov CH, Christensen SL, et al. Prevalence and characteristics of epilepsy in the Belgian shepherd variants Groenendael and Tervueren born in Denmark 1995-2004. *Acta Vet Scand* **50**:51, 2008[0147-50-51]
26. Berendt M, Gullov CH, Fredholm M. Focal epilepsy in the Belgian shepherd: evidence for simple mendelian inheritance. *J Small Anim Pract* **50**:655–661, 2009
27. Thomas WB. Idiopathic epilepsy in dogs. *Vet Clin North Am Small Anim Pract* **30**:206, 2000
28. Bellumori TP, Famula TR, Bannasch DL, Belanger JM, Oberbauer AM. Prevalence of inherited disorders among mixed-breed and purebred dogs: 27,254 cases (1995-2010). *J Am Vet Med Assoc* **242**:1549–1555, 2013
29. Short AD, Dunne A, Lohi H, et al. Characteristics of epileptic episodes in UK dog breeds: an epidemiological approach. *Vet Rec* **169**:48, 2011
30. Weissl J, Hulsmeyer V, Brauer C, et al. Disease progression and treatment response of idiopathic epilepsy in Australian shepherd dogs. *J Vet Intern Med* **26**:116–125, 2012
31. Bielfelt SW, Redman HC, McClellan RO. Sire- and sex-related differences in rates of epileptiform seizures in a purebred beagle dog colony. *Am J Vet Res* **32**:2039–2048, 1971
32. Oberbauer AM, Belanger JM, Grossman DI, Regan KR, Famula TR. Genome-wide linkage scan for loci associated with epilepsy in Belgian shepherd dogs. *BMC Genet* **11**:35, 2010
33. Famula TR, Oberbauer AM, Brown KN. Heritability of epileptic seizures in the Belgian tervueren. *J Small Anim Pract* **38**:349–352, 1997
34. Famula TR, Oberbauer AM. Segregation analysis of epilepsy in the Belgian tervueren dog. *Vet Rec* **147**:218–221, 2000
35. Oberbauer AM, Grossman DI, Irion DN, Schaffer AL, Eggleston ML, Famula TR. The genetics of epilepsy in the Belgian tervuren and sheepdog. *J Hered* **94**:57–63, 2003
36. Kathmann I, Jaggy A, Busato A, Bartschi M, Gaillard C. Clinical and genetic investigations of idiopathic epilepsy in the bernese mountain dog. *J Small Anim Pract* **40**:319–325, 1999
37. Hulsmeyer V, Zimmermann R, Brauer C, Sauter-Louis C, Fischer A. Epilepsy in border collies: clinical manifestation, outcome, and mode of inheritance. *J Vet Intern Med* **24**:171–178, 2010
38. Licht BG, Licht MH, Harper KM, et al. Clinical presentations of naturally occurring canine seizures: similarities to human seizures. *Epilepsy Behav* **3**:460–470, 2002
39. Patterson EE, Armstrong PJ, O'Brien DP, Roberts MC, Johnson GS, Mickelson JR. Clinical description and mode of inheritance of idiopathic epilepsy in English springer spaniels. *J Am Vet Med Assoc* **226**:54–58, 2005
40. Falco MJ, Barker J, Wallace ME. The genetics of epilepsy in the British Alsatian. *J Small Anim Pract* **15**:685–692, 1974
41. Srenk P, Jaggy A, Gaillard C, Busato A, Horin P. Genetic basis of idiopathic epilepsy in the golden retriever. *Tierarztl Prax* **22**:574–578, 1994
42. Casal ML, Munuve RM, Janis MA, Werner P, Henthorn PS. Epilepsy in Irish Wolfhounds. *J Vet Intern Med* **20**:131–135, 2006
43. Wallace ME. Keeshonds: a genetic study of epilepsy and EEG readings. *J Small Anim Pract* **16**:1–10, 1975
44. Hall SJ, Wallace ME. Canine epilepsy: a genetic counselling programme for keeshonds. *Vet Rec* **138**:358–360, 1996
45. Jaggy A, Faissler D, Gaillard C, Srenk P, Graber H. Genetic aspects of idiopathic epilepsy in labrador retrievers. *J Small Anim Pract* **39**:275–280, 1998
46. Berendt M, Gredal H, Pedersen LG, Alban L, Alving J. A cross-sectional study of epilepsy in Danish Labrador Retrievers: prevalence and selected risk factors. *J Vet Intern Med* **16**:262–268, 2002