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Canine epilepsy genetics

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Abstract There has been much interest in utilizing the dog as a genetic model for common human diseases. Both dogs and humans suffer from naturally occurring epilepsies that share many clinical characteristics. Investigations of inherited human epilepsies have led to the discovery of several mutated genes involved in this disease; however, the vast majority of human epilepsies remain unexplained. Mouse models of epilepsy exist, including single-gene spontaneous and knockout models, but, similar to humans, other, polygenic models have been more difficult to discern. This appears to also be the case in canine epilepsy genetics. There are two forms of canine epilepsies for which gene mutations have been described to date: the progressive myoclonic epilepsies (PMEs) and idiopathic epilepsy (IE). Gene discovery in the PMEs has been more successful, with eight known genes; six of these are orthologous to corresponding human disorders, while two are novel genes that can now be used as candidates for human studies. Only one IE gene has been described in dogs, an *LGI2* mutation in Lagotto Romagnolos with a focal, juvenile remitting epilepsy. This gene is also a novel candidate for human remitting childhood epilepsy studies. The majority of studies of dog breeds with IE, however, have either failed to identify any genes or loci of interest, or, as in complex mouse and human IEs, have identified multiple QTLs. There is still tremendous promise in the ongoing canine epilepsy studies, but if canine IEs prove to be as genetically complex as human and murine IEs, then deciphering the bases of these canine epilepsies will continue to be challenging.

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Clinical characteristics of epilepsy in canines and humans

The International League Against Epilepsy (ILAE) has defined an "epileptic seizure" as the transient occurrence of signs due to abnormal excessive or synchronous neuronal activity in the brain, and they define "epilepsy" as a disorder of the brain that is characterized by "an enduring predisposition to generate epileptic seizures" (Fisher et al. 2005). This definition of epilepsy requires the occurrence of at least one epileptic seizure, although it can be argued that to truly be defined as epilepsy, the patient must experience two (therefore, repeated) seizures. The ILAE recently updated their terminology for the etiology of various epilepsies, grouping them into three categories: (1) genetic, indicating that the primary clinical sign is seizures directly resulting from a genetic defect(s), (2) structural/metabolic, indicating that another distinct condition such as infection or trauma has increased the risk of developing epilepsy, and (3) unknown cause, indicating that the underlying mechanism is still unknown and could be genetic or due to another, as yet unrecognized disorder (Berg et al. 2010).

The dog appears to be an excellent model organism for the study of human diseases, particularly complex diseases.

The general hypothesis underlying many such studies is that diseases that are likely caused by the interplay of numerous genes in humans may be caused by fewer genes, or even a single mutation, in dogs. Such a hypothesis assumes that dogs within a breed are more likely to be highly related than individuals in most human populations and, also, that a founder and/or a popular sire effect is likely present. The proof of this concept has been examined in dogs with complex systemic lupus erythematosus (SLE)-related disease (Wilbe et al. 2010). The authors identified five loci associated with the SLE-related disease complex in Nova Scotia Duck Tolling Retrievers, demonstrating that these genetic risk factors are homogeneous within dog breeds. Based on these concepts, research in the form of mapping studies within relatively inbred dog populations and pedigrees segregating naturally occurring epilepsy has been undertaken in an effort to overcome the locus heterogeneity that often plagues human studies for genetic epilepsy.

In both dogs and people, the seizure itself is a result of uncontrolled electrical activity in the cerebral cortex or hippocampus of the brain that can produce a spectrum of behavioral changes, determined by which populations of neurons are firing synchronously. The mildest seizures are absence seizures, which are brief impairments of consciousness: transient cessation of activity with staring and unresponsiveness and no other abnormalities. Such seizures are often missed or not recognized by a dog's owner or the parents of small children. Slightly less mild are focal seizures or partial-onset seizures, which are localized to one small region of the brain and result in the patient losing control of one limb, one half of the body, or the head and neck (sometimes described as fly-biting in dogs). Generalized tonic-clonic seizures are severe and involve the entire cortex from the beginning of the seizure (Lorenz et al. 2011). Patients become tense, convulse, can lose consciousness, fall over, lose control of bowel and bladder, and may not be able to breathe adequately during the muscle tremors and limb paddling. These types of seizures are most easily recognized by others. In the worst cases, generalized seizures can cluster together, requiring hospitalization, or progress to status epilepticus, which is a life-threatening condition where the brain is in a state of persistent seizure and the patient does not completely return to consciousness between seizures (Lorenz et al. 2011). Some cases of focal or partial-onset seizures will progress to generalized seizures. It is particularly difficult to know how often this occurs in canine patients and young children, as the early, focal portion of the seizure is easily missed.

Electroencephalography (EEG) is the recording of electrical activity created by the neurons of the brain. This electrical activity is divided into frequency bands. Wave patterns, including spikes and sharp waves that can be indicative of epilepsy, are observed. EEG is vital for neurologists to diagnose and classify IE in humans, and it allows tight categorization of seizure syndromes. While it has been documented that EEGs in normal and epileptic dogs are possible to record and are similar to those in people (Berendt et al. 1999; Jeserevics et al. 2007; Pellegrino and Sica 2004), EEGs are not commonly performed for dogs. For an EEG to be accurate, the patient must be very still for 2–3 h and, ideally, sleep for a portion of the recording, which is difficult to accomplish in dogs. Using sedation or anesthesia to keep the dog still will substantially affect the EEG. For these reasons, EEGs are not routinely performed in veterinary clinics, and the lack of routine canine EEG recordings makes it difficult to classify canine epilepsy syndromes as precisely as human epilepsy syndromes. The first in vivo, long-term video EEG for a single dog (Poma et al. 2010) was recently reported. Here, sedation was used to place the electrodes, and, once awake, 5 h of video-EEG were obtained on the dog. This allowed a firm diagnosis of absence seizures with myoclonic features and direct comparison to the human syndrome of myoclonic absence epilepsy. Routine use of long-term video EEGs in dogs could vastly improve the accuracy of assigning phenotypes to affected dogs.

The technical beginning of the seizure, the aura, is when abnormalities would first be observed in an EEG on a human. During this stage, which can last for hours and sometimes days and is easily missed by the dog's owner, some affected dogs are restless and insecure—they may seek out their owners or hide (Thomas 2010). The seizure event itself is typically short-lived (seconds to minutes), and recovery after the seizure may include the dog being disoriented, confused, temporarily blind, and occasionally aggressive. Some types of seizures, such as absence seizures, which are difficult to observe in many patients, actually require an EEG for diagnosis.

Epilepsy is not a single disease but encompasses a broad array of disorders and historically has been divided into idiopathic (or primary) or symptomatic (or secondary) disorders (Thomas 2010). Symptomatic, now termed structural or metabolic, epilepsy can result from a rather vast array of causes, including but not limited to metabolic abnormalities, chemical toxicities, neoplasias, infections, and head injuries. Chronic, recurring seizure syndromes with no detectable underlying abnormalities are termed "idiopathic" and are generally presumed to be genetic. Either of the newer classifications "genetic epilepsy" or "unknown epilepsy" could encompass idiopathic epilepsies (IEs). A diagnosis of IE can occur only in canine patients after careful history-taking, physical and neurological examinations, blood chemistry tests, brain imaging, and cerebral spinal fluid analysis have ruled out other causes of recurrent seizure activity. While the majority of

canine IE patients are completely normal between seizures and do not display any other clinical signs (Lorenz et al. 2011), others may express mild abnormalities, such as episodic ataxia, between seizures (Jokinen et al. 2007). Likewise, human IE patients may also display such symptoms between seizures (Imbrici et al. 2004).

Human epilepsy genetics

Much of what is known about the basis and forms of epilepsy comes from studies in human patients. The prevalence of epilepsy in humans is reported to be in the range of 5–10/1,000 in most study settings (Sander 2003), and the subset of these representing idiopathic generalized epilepsies is reported at 15–20% (Jallon and Latour 2005) or up to 40% (Steinlein 1999). IE is now generally accepted to have an underlying genetic origin (Gardiner 2005). There are numerous well-described syndromes of epilepsy that fall into the category of idiopathic generalized epilepsies, such as juvenile absence epilepsy, juvenile myoclonic epilepsy, and epilepsy with grand mal on awakening, all of which have strict clinical and EEG criteria. On occasion, patients can shift from one phenotype to another (Jallon and Latour 2005).

Using careful phenotyping and pedigree analysis, mutations underlying several rare monogenic IEs in humans have been successfully identified. Many of these monogenic IEs are now termed "ion channelopathies" or ion channel disorders, as the mutated genes code for ion channels. Additional mutations have been observed in neurotransmitter receptor genes. For example, *SCN1B*, the gene for the voltage-gated sodium channel, beta subunit, has been implicated in generalized epilepsy with febrile seizures plus (GEFS+), an autosomal dominant epilepsy. In one large Australian family with 26 members having epilepsy consistent with GEFS+ syndrome, linkage analysis found that the disorder segregated to HSA 19q13.1, where the strong candidate gene *SCN1B* was located (Wallace et al. 1998) and a single nucleotide point mutation was found. Subsequent functional studies in frog oocytes for this mutation showed slower sodium channel inactivation, likely causing inward neuronal sodium currents that would increase membrane depolarization and neuronal hyperexcitability, predisposing the patient to seizures. However, overlapping GEFS+ syndromes can result from mutations in additional genes, i.e., *SCN1A*, *SCN2A*, and *GABRG2* (Gardiner 2005; Meisler et al. 2001). Mutations in *GABRG2* have also been associated with the phenotype of childhood absence epilepsy and febrile seizures (Wallace et al. 2001). Many other human IE phenotypes have been linked to or associated with mutations in ion channels, including additional GABA receptors as well as calcium channels, potassium channels, a chlorine channel, and acetylcholine receptors. These have been reviewed elsewhere (Gurnett and Hedera 2007; Poduri and Lowenstein 2011).

Non-ion-channel genes have been implicated in IEs, where their involvement in the neural system and their implications in seizures may not always be obvious. For example, 25 different mutations have been identified in the gene *LGI1* (leucine-rich glioma inactivated-1) that have been associated with autosomal dominant lateral temporal epilepsy or autosomal dominant partial epilepsy with auditory features (Nobile et al. 2009). The function of this gene was unknown until 2006, when it was discovered that the product of *LGI1* interacts with the potassium channel encoded by *KCNA1* (Schulte et al. 2006). LGI1 was shown to normally upregulate KCNA1 potassium channels by preventing their rapid inactivation by KCNAB1. Mutations in *LGI1* abolish the antagonizing effect of KCNAB1 and result in an overall increase in KCNA1 channel activity. More recent work suggests that this gene also plays an important role in neurodevelopment via pruning and maturation mechanisms at the neuron terminal (Zhou et al. 2009). The handful of other non-ion-channel genes involved in IEs are discussed in other reviews (Gurnett and Hedera 2007; Poduri and Lowenstein 2011; Turnbull et al. 2005), and many represent new protein classes involved in IE.

For a far more complete discussion of the genetics of human epilepsy, readers should consult recent reviews (Baulac and Baulac 2009; Gardiner 2005; Greenberg and Pal 2007; Gurnett and Hedera 2007; Turnbull et al. 2005). Despite these advances, the genetic bases for the majority of human IEs remain unsolved and are typically referred to as the common or complex non-Mendelian IE syndromes. The fact that replicate studies in different families/populations suffering similar types of seizures do not always reveal similar mutations reemphasizes that there are most likely many genes responsible for epilepsy.

Murine epilepsy genetics

The most commonly used animal model for genetic epilepsy disorders is the mouse. Dozens of genes have been identified in which mutations cause epileptic seizures in mice, most of which have been intentionally knocked out; only a handful have arisen spontaneously (McNamara and Puranam 1998; Meisler et al. 2001). Not surprisingly, many of the genes are ion-channel genes, including the calcium channel and potassium channel gene families. For example, the *stargazer* mouse has a mutation in the calcium channel gene *Cacng2* (Frankel 1999) and the *tottering* mouse has a mutation in the calcium channel gene *Cacna1a* (Fletcher

et al. 1996). In fact, the *tottering* mouse is an excellent example of a mutated orthologous gene causing a similar phenotype in different species: spontaneously arising mutations in *Cacna1a* in the mouse create the *tottering* phenotype of nonconvulsive generalized spike-wave discharges on EEG that resemble human absence seizures (Todorova and Seyfried 2006). Additional mouse models with mutations in this same gene exist and include the leaner, rocker, and rolling lines. The involvement of *CACNA1A* in human absence epilepsy was validated in patients with absence seizures and episodic ataxia (Imbrici et al. 2004; Jouvenceau et al. 2001). Another example of an orthologous mutated gene is the voltage-gated potassium channel gene *KCNA1*. In humans, several different point mutations in *KCNA1* have been associated with episodic ataxia type 1 (EA1). While EA1 is not primarily an epileptic disorder, some patients exhibit partial epilepsy. In fact, a spectrum of seizure phenotypes is observed with these *KCNA1* mutations, from benign partial seizures during infancy to generalized motor seizures (Eunson et al. 2000; Zuberi et al. 1999). In mice, the disruption of the orthologous gene causes frequent spontaneous seizures throughout the life of the mouse (Smart et al. 1998; Todorova and Seyfried 2006). As in humans, additional non-ion-channel genes have also been implicated in spontaneous epilepsy in mice (Meisler et al. 2001). A full discussion of specific mouse mutations resulting in epileptic phenotypes is not undertaken in the present review.

There are also complex trait epilepsy models in mice. The EL (epilepsy-like) mouse strain can have seizure activity induced by physical stimulation, such as moving mice from cage to cage, and suffers generalized tonic-clonic seizures or complex partial seizures with secondary generalization (Frankel 1999). Several genetic segregation and mapping studies have shown unambiguously that more than one genetic locus influences seizures in EL mice (Flavin and Seyfried 1994; Frankel et al. 1995a, b; Rise et al. 1991). This mouse model of epilepsy has all the hallmarks of a polygenic complex phenotype, with at least six different loci that apparently contribute to the seizure susceptibility. Gene interaction, locus heterogeneity, and gene-by-environment interaction have all been observed. In one study of this strain, a quantitative trait locus (QTL) was revealed in a 1-cM interval; however, additional dissection revealed multiple loci (Legare et al. 2000). The authors conceded that discerning the underlying genetics of polygenic neurological behaviors is difficult, even in inbred strains.

Finally, a special case of murine epilepsy deserves discussion. A missense mutation in dynamin-1 (*DNM1*) in the fitful mouse model causes recurrent seizures in its heterozygous form and more severe to lethal disease in its homozygous form (Boumil et al. 2010). This was the first study to identify a *DNM1* mutation that led to epilepsy. Interestingly, a recessive missense mutation in exon 6 of *DNM1* was previously described in several breeds of dog. This mutation was highly associated not with seizures, but with a reversible collapse phenotype of flaccid paraparesis and loss of control of the rear limbs, with potential progression to the forelimbs (Patterson et al. 2008). Dynamin-1 functions in fission of endocytic vesicles from the plasma membrane, and the fact that these very different phenotypes result from different mutations in the same gene suggests that there are many additional potential epilepsy-associated candidate genes that may not be immediately apparent.

Canine epilepsy genetics

It has been argued that dog populations may be more likely to have a founder effect underlying many of their complex phenotypes, and that the genetic basis for diseases such as inherited epilepsies could potentially be less complex in dogs than in humans (Ostrander and Kruglyak 2000; Lindblad-Toh et al. 2005). As such, there has been keen interest in utilizing the dog breed models of inherited epilepsy as large animal models for this disease in humans. Using the dog model of epilepsy might allow identification of new genes involved in central nervous system function as well as novel genes involved in human inherited epilepsies with more ease than in comparable human genetic studies.

Breeds with suggested inherited idiopathic epilepsies

The prevalence of canine IE, based on a nonreferral population, is reported to be between 0.5 and 5% (Podell et al. 1995), which makes dogs the domesticated species with the highest prevalence of spontaneously occurring epilepsy (Loscher 1997). The prevalence of epilepsy can be much higher in specific breeds; for example, in the Belgian Shepherd Tervueren and Groenendael variants, the prevalence was estimated in one study to be 9.5% (Berendt et al. 2008), and in one extended Belgian Shepherd family, the prevalence of epilepsy has been reported as high 33% (Berendt et al. 2009). There is a growing body of literature to support the hereditary basis for IE in many breeds, with a variety of genetic inheritance models proposed. Most IEs in dogs are thought to be genetically based (Thomas 2000), and IE has been reported in nearly every dog breed as well as in mixed-breed dogs.

Many breeds with a high prevalence of IE have been studied closely. A genetic or familial hereditary basis for IE has been investigated and proposed for each of the breeds listed in Table 1, typically by describing the clinical

Table 1 Breeds with suggested inherited idiopathic epilepsy

Breed	Seizure characteristics	Age of onset	Genetic basis	Sex influence	References
Beagle	Partial and generalized	1 year minimum	Significant sire effect	Bias toward males	Bielfelt et al. (1971)
Belgian Shepherd	Most focal onset, some with secondary generalization	Mean of 3.3 years	Simple Mendelian, likely autosomal	No bias	Berendt et al. (2009)
Belgian Shepherd	Generalized	Mean of 4 years	Polygenic	No bias	Oberbauer et al. (2010)
Belgian Tervueren	Not reported	Widely variable	Hereditary basis, single-locus models not adequate to explain	No bias	Famula et al. (1997)
Belgian Tervueren	Not reported	Not reported	Suspected single locus of large effect, with complex pattern of inheritance	No bias	Famula and Oberbauer (2000)
Belgian Tervueren and Sheepdog	Generalized	Not reported	Polygenic	No bias	Oberbauer et al. (2003)
Bernese Mountain Dog	Most generalized	1–3 years	Polygenic autosomal recessive, sex-modified	Bias toward males	Kathmann et al. (1999)
Border Collie	Generalized, many with initial focal onset	Under 5 years	Autosomal recessive, or more complex and resembling recessive	No bias	Hulsmeyer et al. (2010)
Dalmatian	Most partial onset with secondary generalization	3 years	Not determined	Slight bias toward females	Licht et al. (2002)
English Springer Spaniel	Partial and generalized	Under 6 years	Partially penetrant autosomal recessive or polygenic	No bias	Patterson et al. (2005)
German Shepherd Dog (British Alsatian)	Not reported	1–2 years	Sire effect and affected dogs more inbred	Bias toward males	Falco et al. (1974)
Golden Retriever	Most generalized	1–3 years	Polygenic autosomal recessive	Bias toward males	Srenk et al. (1994)
Irish Wolfhound	Generalized	Under 3 years	Incompletely penetrant recessive, with sex predilection	Bias toward males	Casal et al. (2006)
Keeshond	Not reported	1 year minimum	Hereditary basis	Bias toward males	Wallace (1975)
Keeshond	Not reported	Not reported	Suspected single autosomal recessive	No bias	Hall and Wallace (1996)
Labrador Retriever	Most generalized with possible partial onset	1–3 years	Polygenic autosomal recessive	No bias	Jaggy et al. (1999)
Labrador Retriever	Partial and generalized	Under 4 years	Not determined	No bias	Berendt et al. (2002)
Standard Poodle	Most partial onset with secondary generalization	3 years	Not determined	No bias	Licht et al. (2002)
Standard Poodle	Most partial onset, with occasional secondary generalization	Under 7.5 years	Simple autosomal recessive, with complete or nearly complete penetrance	No bias	Licht et al. (2007)
Vizsla	Partial and generalized	1–3 years	Autosomal recessive, possibly polygenic	No bias	Patterson et al. (2003)

Breeds listed are those that have been described in the literature and best fit the definition of true IE. Characteristics of the seizure syndromes in each breed are listed, as well as the most specific speculated mode of inheritance provided by the reference publication

phenotype, examining the pedigrees, and suggesting a potential mode of inheritance. The Lagotto Romagnolo is the first published genetic IE model and is discussed further below. Additional breeds, such as Australian Shepherds, Norwich Terriers, and Greater Swiss Mountain Dogs, to name a few, are also subjects of investigation into IE, but clinical descriptions and possible modes of inheritance for these breeds have not yet been published. There may be a lack of sufficient information for other breeds suffering epilepsy to be definitively classified as having IE or even

an inherited epilepsy syndrome; these include the Boxer and Shetland Sheepdog. Epilepsy has been reported in the Boxer and was determined to have medium to high heritability (Nielen et al. 2001). This report did not, however, indicate that the epilepsy cases underwent thorough testing and follow-up to rule out nonheritable causes of seizures, creating uncertainty as to the accuracy of a true IE diagnosis. Epilepsy in the Shetland Sheepdog appears to be inherited in a multifactorial or autosomal dominant fashion (Morita et al. 2002). Affected dogs in this study had histopathological changes in their brain tissue and it is currently unknown if these lesions resulted from primary pathology or from the seizures only; in the latter case this could be classified as IE. Finally, a genetic epilepsy has been reported in the Finnish Spitz (Jeserevics et al. 2007; Viitmaa et al. 2006), including EEG findings, but pedigree analysis and mode of inheritance has yet to be published.

Among the IE studies utilizing pedigree segregation analysis, there has been evidence for an autosomal recessive inheritance or a gene of major effect, both of which could occur due to founder effect. However, many studies could not rule out polygenic inheritance. For example, in a study of IE in English Springer Spaniels, the mode of inheritance appeared to be partially penetrant autosomal recessive or polygenic (Patterson et al. 2005). Similarly, in Vizslas, segregation analysis showed that IE in this breed is likely inherited in an autosomal recessive manner, but polygenic inheritance could not be excluded (Patterson et al. 2003).

IE seizure phenotypes vary among breeds; IE in some breeds manifests more frequently as focal onset seizures, whereas in others seizures are mostly generalized. The frequency of epileptic dogs suffering cluster seizures and status epilepticus also varies. Taken together, it is clear that as in humans, multiple IE loci will exist in dogs, some of which may be simple and others complex, and that more than one locus is likely to exist for IE in many dog breeds.

IE seizure disorders with known mutations

The Lagotto Romagnolo breed segregates a recessive benign familial juvenile epilepsy (Jokinen et al. 2007), which typically remits by 4 months of age (Table 2). The genetic cause for this syndrome has recently been identified as a truncating mutation in *LGI2*, an ortholog of the human epilepsy gene *LGI1* (Seppala et al. 2011). This first canine IE gene sheds new light on the mechanisms of neuronal synaptic network remodeling during development, and shows that there is time sensitivity in the expression of *LGI1* and *LGI2*, though they act on some of the same ADAM receptors. The Lagotto Romagnolo IE mutation discovery is particularly important because it is the first known canine epilepsy mutation directly linked to remission, it is developmentally stage-specific, and it sheds light on a novel pathway resulting in epilepsy.

Progressive myoclonic epilepsies with known mutations

The progressive myoclonic epilepsies (PMEs) are characterized by progressive neurological decline. These seizure disorders are not technically defined as IE, since the dogs often have abnormal mentation between seizure episodes and the disease process is both progressive and degenerative. In addition, abnormal metabolites may be measured in affected individuals and histopathologic abnormalities may be observed postmortem. Investigations of several dog breeds with inherited PMEs have met with success, and they have highlighted the sharing of mutations in orthologous genes creating similar disease in both humans and dogs.

In 2005, the mutation causing autosomal recessive PME known as Lafora disease (EPM2) in Miniature Wirehaired Dachshunds was published (Lohi et al. 2005). The disease is the result of a biallelic expansion of a dodecamer repeat in the *EPM2B* gene, which the team identified using homozygosity mapping and linkage analysis. Histopathologic changes are observed in affected dogs as intracellular Lafora bodies in multiple tissues, including the brain, muscle, liver, and heart (Harriman et al. 1955; Serratosa et al. 1995). Lafora disease is also observed in humans, and mutations for this disease have been found in the laforin (*EPM2A*) gene (Minassian et al. 1998) and the malin gene (*NHLRC1*, also called *EPM2B*) (Chan et al. 2003; Gomez-Abad et al. 2005). This is a clear demonstration of an orthologous gene being mutated in two species and causing similar clinical disease.

The neuronal ceroid lipofuscinoses (NCLs) are a group of inherited PMEs resulting from lysosomal storage disorders. They cause epileptic seizures, along with other clinical signs, and are characterized by accumulation of autofluorescent lysosomal storage bodies. NCLs are observed in human patients as well as several breeds of dog, and mutations have now been described for eight canine NCLs, which are summarized in Table 2.

First described was a missense mutation in *CLN8* in English Setters with NCL (Katz et al. 2005). Mutations have been observed in this gene in human NCL patients as well, although these patients vary in the speed of the progression of their disease and their actual symptoms (Ranta et al. 1999, 2004). Nearly simultaneously, a *CLN5* mutation was described in Border Collies suffering NCL (Melville et al. 2005). A human NCL variant with mutation of *CLN5* exists, having a clinical picture similar to that seen in the Border Collies, except that few human patients exhibited behavioral problems, whereas this was common in the canine patients. Next, a missense mutation in *CTSD* was described in American Bulldogs with NCL (Awano

Table 2 Breeds with known genetic epilepsy

Breed	Type	Category	Age of onset	Gene mutated	Type of mutation	Genetic basis	Human orthologous disease	References
Lagotto Romagnolo	Remitting	IE	5–9 weeks	*LGI2*	Nonsense	Autosomal recessive	Novel gene, but mutations known in *LGI1* in human IE patients	Seppala et al. (2011), Jokinen et al. (2007)
Miniature Wire Haired Dachshund	EPM2 (Lafora disease)	PME	6–9 years	*EPM2B*	Dodecamer repeat expansion	Autosomal recessive	Yes, *EPM2B* mutations in human Lafora disease patients	Lohi et al. (2005)
English Setter	NCL	PME	1–2 years	*CLN8*	Missense	Autosomal recessive	Yes, *CLN8* mutations in human NCL patients	Katz et al. (2005)
Border Collie	NCL	PME	Varies, but may be as early as 15 months	*CLN5*	Nonsense	Autosomal recessive	Yes, *CLN5* mutations in human NCL patients	Melville et al. (2005)
American Bulldog	NCL	PME	Before 2 years	*CTSD*	Missense	Autosomal recessive	Yes, *CTSD* mutations in human NCL patients	Awano et al. (2006b), Evans et al. (2005)
Dachshund	NCL	PME	At 9 months	*TPP1*	Single nucleotide deletion	Autosomal recessive	Yes, *CLN2*, the human ortholog of canine *TPP1*, mutations in human NCL patients	Awano et al. (2006a)
American Staffordshire Terrier	NCL	PME	3–5 years	*ARSG*	Nonsynonymous substitution	Autosomal recessive	Novel gene, candidate for human late-onset NCLs	Abitbol et al. (2010)
Dachshund	NCL	PME	<9 months	*PPT1*	Single nucleotide insertion	Autosomal recessive	Yes, *PPT1* mutations in human NCL patients	Sanders et al. (2010)
Australian Shepherd	NCL	PME	<2 years	*CLN6*	Missense	Autosomal recessive	Yes, *CLN6* mutations in human NCL patients	Katz et al. (2011)
Tibetan Terrier	NCL	PME	Adult onset	*ATP13A2*	Single nucleotide deletion	Autosomal recessive	Yes, *ATP13A2* mutations in human patients, but they are not recognized as NCLs	Farias et al. (2011)

Breeds listed are those that have been described in the literature with known genetic mutations causing their epilepsy

IE idiopathic epilepsy, *NCL* neuronal ceroid lipofuscinosis, *PME* progressive myoclonic epilepsy

et al. 2006b). At the time, sheep and knockout mice were the only species with reported *CTSD* mutations, but, almost immediately, mutations in this gene were reported in two cases of human NCLs (Siintola et al. 2006; Steinfeld et al. 2006). Also that year, the mutation underlying a case of Dachshund NCL was published (Awano et al. 2006a). In this instance, a single nucleotide deletion predicted a frameshift and premature stop codon in canine *TPP1*. This gene is the ortholog of human *CLN2*, which was already known to be mutated in human NCL.

Four more canine NCL mutations have been recently described. The American Staffordshire Terriers (ASTs) segregate an adult-onset NCL similar to the human adult-onset NCLs, known as Kufs' disease. The ASTs were shown to have a nonsynonymous substitution in *ARSG*, and this gene represents a novel candidate gene for Kufs' patients (Abitbol et al. 2010). A second NCL mutation was then described in the Dachshund breed, this time in *PPT1*, a well-known gene definitively associated with human NCL (Sanders et al. 2010). Next, a missense mutation in *CLN6* was described in a single Australian Shepherd, with one additional likely case also homozygous for this mutation (Katz et al. 2011). *CLN6* is another well-known gene associated with human NCL. Most recently, a single nucleotide deletion was described in *ATP13A2* in Tibetan Terriers that predicts a premature stop codon (Farias et al. 2011). Intriguingly, while this mutation clearly causes an NCL in the Tibetan Terriers, similar truncating mutations

in the human ortholog cause Kufor-Rakeb syndrome (KRS), a neurodegenerative disorder that is not classified as an NCL. Furthermore, the phenotypes only partially overlap between the diseases in these two species: the Tibetan Terrier phenotype more closely mirrors Kufs' disease than KRS. To date, eight different genes have been reported in human cases of NCL (Jalanko and Braulke 2009), six of which have now been described in canine NCLs (*PPT1*, *TPP1* or *CLN2*, *CLN5*, *CLN6*, *CLN8*, and *CTSD*). Two of the canine NCL genes (*ARSG* and *ATP13A2*) are now established as excellent candidates for unsolved human NCLs. The canine genetic NCL epilepsies provide animal models of human genetic NCLs and deepen our understanding of neurodegeneration, particularly in the instance where mutations in orthologous genes have produced different phenotypes.

IE candidate gene studies

One recent candidate gene study examined four dog breeds for association or linkage to microsatellite markers in genes already known to be involved in human or murine IE (Ekenstedt et al. 2011). This study examined 52 genes encoding mostly ion channels and neurotransmitters in Beagles, Greater Swiss Mountain Dogs, English Springer Spaniels, and Vizslas and found no major associations or linkages to IE in any breed. While the original hypothesis was that a founder effect might be occurring in one or more of these breeds, it is difficult to draw major conclusions from this study other than likely ruling out plausible candidate genes in specific instances. An additional, as yet unpublished study also utilized a candidate gene approach, selecting 118 SNPs in 19 ion channel genes and examining them for association to IE in 18 pedigree breeds as well as in crossbreeds. Several statistically significant associations were reported and were confirmed with replication cohorts. Some of the associations were breed-specific, while others were common to multiple breeds (A. Short, personal communication).

One critical issue facing candidate gene analyses of these types is the occurrence of false positives and false negatives that can result from sampling bias and population stratification. One way to control for this confounding is to address the degree of relatedness by utilizing discordant sibling pairs, ideally full siblings. These case and control pairs should differ at the disease locus but share most other portions of the genome.

IE genome-wide linkage studies

Genome-wide linkage studies have been undertaken in several dog breeds, although many remain unpublished, likely due to inconclusive or negative data. For example, our group undertook a genome-wide linkage scan utilizing DNA from 96 Vizslas, of which 31 were classified as epileptic, representing two large extended families. More than 500 microsatellite markers were included, and though there were five regions of suggested linkage (LOD > 1.0), none achieved a LOD score > 3.0, which is considered significant evidence for linkage (Ekenstedt 2010). A similar, recently published study by Oberbauer et al. (2010) utilized DNA from 366 Belgian Shepherd dogs, 74 of which were epileptic, from two extended family pedigrees. This genome-wide linkage scan used 410 microsatellite markers and identified six QTLs on four chromosomes that appeared to be tentatively linked to IE, with no LOD scores achieving classical significance in excess of 3.0 (Oberbauer et al. 2010). An earlier study by the same group (Oberbauer et al. 2003), that used fewer dogs and fewer markers, also did not achieve significant LOD scores; they identified three genomic regions with nominal linkage to the epileptic phenotype. These studies begin to underscore the complexity of IE in Vizslas and Belgian Shepherds, as previously published segregation analyses in both breeds suggested, respectively: autosomal recessive inheritance (although polygenic inheritance could not be excluded) (Patterson et al. 2003) and a single locus with a large effect with a further complex pattern of inheritance (Famula and Oberbauer 2000). It is possible that microsatellite studies lacked the resolution to clearly identify IE-associated regions or that underlying assumptions regarding the genetic model were incorrect.

IE genome-wide association studies

Genome-wide association studies (GWASs) for IE are being conducted with high-density canine SNP arrays in multiple breeds. Unfortunately, many of these remain unpublished because the results do not achieve genome-wide significance. For example, our group, in conjunction with the LUPA initiative, has conducted a GWAS with IE-affected ($n = 47$) and unaffected ($n = 48$) Vizslas using the Affymetrix 50 k canine SNP array and failed to identify any loci of major effect (Ekenstedt 2010). We have also conducted a GWAS with English Springer Spaniels, first with the Illumina 22 k canine SNP arrays (cases, $n = 53$; controls, $n = 91$) (Ekenstedt 2010), and subsequently with the Illumina 170 k canineHD SNP arrays (cases, $n = 24$; controls, $n = 24$) (K. J. Ekenstedt, unpublished data), and again failed to identify any loci of major effect. Others, specifically the LUPA initiative, have reportedly had more success: novel IE loci have been mapped via GWAS to several different chromosomes for various breeds, including the Belgian Shepherd, Norwich Terrier, Border Terrier, Schipperke, and Finnish Spitz, although specific mutations have not yet been described (Lequarre et al. 2011). All of these loci, interestingly, are devoid of known epilepsy genes. However,

many of the other breeds subjected to GWAS in the LUPA IE studies have not revealed any significant findings, suggesting that many of these canine IEs are oligogenic. A large meta-analysis is underway on the combined data set to attempt to identify loci that may be shared across breeds (H. Lohi, personal communication).

The progression of canine genomic tools from 22 k on to 170 k SNP arrays, along with technological improvements that increase genotyping rate and accuracy, has undoubtedly had an impact on the successes and failures of these studies. It is possible that earlier studies utilizing microsatellites or fewer SNPs failed to detect true IE loci or did not detect all involved loci.

Pharmacogenetics and canine IE

In addition to the search for disease-causing mutations, investigations into the genetics of drug response and drug resistance in canine IE are ongoing. One recently published study of epileptic Border Collies examined the *ABCB1* gene (also called the *MDR1* or multidrug resistance 1 gene). Affected dogs in this breed are often poorly controlled with antiepileptic drugs, and resistant epilepsy develops in up to 71% of the cases (Hulsmeyer et al. 2010). It was determined that a sequence variation in *ABCB1* intron 1 is associated with drug responsiveness in this breed (Alves et al. 2011). A previous study that pooled many breeds of epileptic dogs together used a custom SNP BeadChip containing 30 genes involved in drug metabolism, drug targeting, and drug transport to identify those associated with phenobarbital drug response (the usual first line of treatment for canine epilepsy) (Kennerly et al. 2009). Five genes were identified that while not significant after adjustment for multiple comparisons, were suggestive of association with drug response; not surprisingly, two were ion channels (*KCNQ3* and *SCN2A2*) and one was a neurotransmitter receptor (*GABRA2*). Further replication and breed-specific analysis is clearly required, and it appears, at least initially, that the pharmacogenetic drug response studies might also be complex.

Canine IE: future prospects

Clearly, much work in the field of canine epilepsy genetics remains to be done and many questions remain to be answered. The initial hypothesis that many dog breed IEs would be caused by a single gene due to a founder effect no longer seems to be supported. Rather, it appears that canine IE is much more likely to be polygenic, as are most human IEs. The absence of robust associations in numerous studies certainly supports this conclusion. Nevertheless, nine genes have now been described that are involved in canine epilepsies (one for IE and eight for PMEs). The hypothesis that many of the genes would be identical to those in human epilepsies has been proven to some extent, with many of the known canine epilepsy genes being orthologous to those in humans, although the phenotypes are not always identical. Canine epilepsy genetic research has also provided new candidate genes for human studies and has deepened our knowledge about neurotransmission and neurodevelopment. There are also now genetic tests for the known genetic epilepsies in dogs, which can be used as tools to decrease disease in their breeds.

There are also other potential confounding factors to consider. Seizure characterization is of the utmost importance, and owner-reported information is fraught with inconsistencies, making it nearly impossible to universally properly classify seizures into an appropriate category. Subtle differences in seizure presentation may actually represent different underlying genetic causality, and if these are inadvertently pooled, this may prevent identification of associated genes. Human epilepsy encompasses over 40 different syndromes, specifying age of onset, seizure stimuli, seizure characteristics, and EEG abnormalities. Clearly, there is room for improvement in the accuracy of canine seizure phenotypes into more tightly defined syndromes. Development of standardized case definitions would be significantly aided if epileptic dogs routinely underwent EEG examination, although practically, it may be difficult to obtain this level of diagnostic workup in every case. Unaffected dogs likewise deserve close scrutiny and should be followed until their demise for absolute seizure-free classification, and ideally they should also undergo EEG examination before being included in genetic studies as controls for IE.

It has already been shown in the case of the Lagotto Romagnolo (Seppala et al. 2011) that within a single breed there is more than one form of genetic epilepsy. In fact, the genetics involved in canine IE could even be distinctly different between lines in a breed, as has been suggested for the Poodle (Licht et al. 2007). Or, it is possible that the predisposition for epilepsy may actually be fixed in some breeds, and expression of the trait is due to modifying genes and/or environmental influence. It seems likely that should susceptibility loci eventually be identified for breed-specific canine IEs, they may not be fully penetrant and may involve environmental influences. This is also seen within the Vizsla and English Springer Spaniel pedigrees, where a proportion of the dogs in each breed had different seizure characteristics (Patterson et al. 2003, 2005).

Other polymorphisms that are coming under increased scrutiny in canine and human disease etiology are copy number variations (CNVs). CNVs are an abundant source of polymorphism, estimated to affect at least 10% of the genome (Redon et al. 2006; Wong et al. 2007). CNVs have

been proposed as one determinant to explain varied disease penetrance and phenotypic variability among inherited disorders (Beckmann et al. 2007). Microdeletions have already been shown to increase the risk of idiopathic generalized epilepsy in some human patients (de Kovel et al. 2010; Dibbens et al. 2009; Helbig et al. 2009). In one whole-genome CNV analysis, the authors identified nearly 9% of their proband IE cases as having copy number changes (Mefford et al. 2010) and in another analysis, large deletions (100 kb or larger) at HSA 16p13.11 were shown to be the single greatest genetic risk factor for overall seizure susceptibility (Heinzen et al. 2010). Furthermore, it is known that using SNPs in association studies for CNV-related cases can fail to identify the causative genomic regions, as the SNPs will not be in Hardy–Weinberg equilibrium or will fail Mendelian inheritance verification, particularly in multiallelic CNVs (Beckmann et al. 2007). The first canine CNV studies have been published (Chen et al. 2009; Nicholas et al. 2009, 2011); they provide a valuable tool for assessment of genetic variation contributing to disease. It is already known that duplication variations underlie the hair ridge in Rhodesian Ridgeback dogs (Salmon Hillbertz et al. 2007) as well as familial Shar-Pei fever (Olsson et al. 2011). It is therefore likely that combining traditional GWAS SNP studies with CNV analyses, such as high-density array comparative genomic hybridization studies, will help elucidate some of the canine IEs that GWAS SNP studies alone have failed to solve. Finally, in addition to CNV analysis, future studies may require moving from traditional Sanger sequencing technologies, applied to a population of cases and controls, to whole-genome sequencing technologies on an individual dog basis.

The pace of genetic research has been rapid but canine epilepsy genetics have proven to be more complex than originally anticipated. Though the genetic basis for a handful of forms of epilepsy in the dog, such as Lafora disease, has been described, many remain unsolved. The parallels between canine and human epilepsy genetics are striking, and canine studies may need to move in the same direction as human studies, i.e., significantly increase the number of samples, move to whole-exome and whole-genome sequencing of individual dogs, and add CNV companion studies to existing GWAS studies.

Identifying the underlying molecular mechanisms of IE in dogs still poses a challenging and formidable task, but the promise of identifying chromosomal loci involved in canine IE brings hope for additional candidate gene studies in humans, possible molecular screening susceptibility tests for dog breeders, increasing our understanding of the pathophysiology of neuronal hyperexcitation, and potentially even the development of novel pharmaceutical and gene therapies for IE in both species.

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