Paroxysmal Dyskinesia in Border Terriers: Clinical, Epidemiological, and Genetic Investigations


Background: In the last decade, a disorder characterized by episodes of involuntary movements and dystonia has been recognized in Border Terriers.

Objectives: To define clinical features of paroxysmal dyskinesia (PD) in a large number of Border Terriers and to study the genetics of the disease.

Animals: 110 affected and 128 unaffected client-owned Border Terriers.

Methods: A questionnaire regarding clinical characteristics of PD was designed at Utrecht University and the University of Helsinki. Thirty-five affected Border Terriers underwent physical examination and blood testing (hematology and clinical biochemistry). Diagnostic imaging of the brain was performed in 17 affected dogs and electroencephalograms (EEG) between episodes were obtained in 10 affected dogs. A genomewide association study (GWAS) was performed with DNA of 110 affected and 128 unaffected dogs.

Results: One hundred forty-seven questionnaires were included in the study. The most characteristic signs during episodes were dystonia, muscle fasciculations, and falling over. The majority of owners believed that their dogs remained conscious during the episodes. A beneficial effect of anti-epileptic therapy was observed in 29 of 43 dogs. Fifteen owners changed their dogs’ diet to a hypoallergenic, gluten-free diet, and all reported reasonable to good improvement of signs. Clinical examinations and diagnostic test results were unremarkable. The GWAS did not identify significantly associated chromosome regions.

Conclusions and Clinical Importance: The survey results and EEG studies provided further evidence that the observed syndrome is a PD rather than epilepsy. Failure to achieve conclusive results by GWAS indicates that inheritance of PD in Border Terriers probably is complex.

Key words: Canine; CECS; Episodic movement disorder; Spike’s disease.

Abbreviations:
CD celiac disease
CECS canine epileptoid cramping syndrome
CT computed tomography
EEG electroencephalography
GWAS genomewide association study
MRI magnetic resonance imaging
PD paroxysmal dyskinesia
PED paroxysmal exertion-induced dyskinesia
PKD paroxysmal kinesigenic dyskinesia
PNKD paroxysmal nonkinesigenic dyskinesia
SNP single nucleotide polymorphism

Paroxysmal dyskinesias (PDs) are rare movement disorders characterized by recurrent episodes of involuntary hyperkinetic movements, altered muscle tone and a variable phenotype. A key feature is preserved consciousness during the attacks. Based on triggering events, frequency, duration, and characteristics of the hyperkinetic episodes, 3 distinct types of PDs are recognized in human medicine: (1) paroxysmal kinesigenic dyskinesia (PKD) in which the attacks are induced by abrupt voluntary movements, (2) paroxysmal nonkinesigenic dyskinesia (PNKD) in which the attacks are not preceded by sudden movement or exercise, and (3) paroxysmal exertion-induced dyskinesia (PED) in which attacks are triggered by prolonged physical exercise. All forms can be primary with a suspected or known genetic etiology or secondary to other disorders such as multiple sclerosis and head trauma. In the last decade, causative mutations in the
following genes have been identified for all of the above-mentioned types: PRRT2 for PKD, PNKD (MR-1) and KCNMA1 for PNKD, and SLC2A1 (GLUT1) for PED.4–7

Initially, PDs (and especially PKD) were regarded as a type of focal epilepsy based on brief paroxysmal attacks, frequent premonitory sensations, and dramatic positive response to anti-epileptic drugs in PKD. However, over the last few decades, many authors favor the hypothesis that they represent nonepileptic movement disorders because of normal interictal and ictal electroencephalography (EEG) findings in most patients, maintained consciousness and the absence of a post-ictal phase.8,9

Paroxysmal dyskinesias are increasingly recognized in dogs. Both sporadic and familial cases of (suspected) paroxysmal dyskinesia have been reported.10–13 A deletion in the BCAN gene was identified as the cause of Episodic Falling Syndrome, a paroxysmal hypertonicity disorder, in Cavalier King Charles Spaniels.14,15

Recently, phenotypic characteristics of a suspected paroxysmal dyskinesia, referred to as canine epileptoid cramping syndrome (CECS), were described in 29 Border Terriers in which clinical features resembled PNKD.16 However, no EEG studies were performed. In the past decade, “cramping episodes” also have been reported by breeders and owners of specific families of Border Terriers in the Netherlands and Germany. During the same time frame, an increasing number of Border Terriers with episodic dystonia was observed in Finland. Clinical and genetic investigations were begun at the Veterinary Faculty of the University of Helsinki (Finland) and the Utrecht University (the Netherlands).

Correct phenotyping is essential for genetic studies, but can be challenging in paroxysmal disorders with variable clinical presentation, and unknown pathophysiology. The goal of our study was to thoroughly characterize clinical signs in a large number of affected Border Terriers, describe diagnostic features (including EEG findings), establish prevalence, and investigate genetic aspects of “cramping episodes” in Border Terriers. For this purpose, results from Dutch and Finnish studies were combined.

Materials and Methods

Prevalence Studies

A general health surveillance survey in a cohort of Border Terriers was initiated by the Dutch Border Terrier club in 2004. A comprehensive questionnaire concerning health and behavior was designed and sent to owners of 1126 Dutch Border Terriers born between 1998 and 2001. One of the questions was whether the dog had experienced episodes of abnormal movements or posture. Five years later, the study was repeated and owners of 1494 Dutch Border Terriers born between 2003 and 2006 were invited to complete the survey. The results of the general health surveillances were used to estimate the prevalence of PD.

Questionnaire on PD

In the Netherlands and Finland, an extensive questionnaire on PD was developed. Because the 2 surveys were designed independently, they were not identical. However, both surveyed sex, age of onset, episode characteristics, signs immediately before and after episodes, possible predisposing factors, and average number and duration of episodes. Information on medical history, treatment, and diet also was collected. The Dutch questionnaire differed from the Finnish questionnaire in that it also requested owners to judge the effect of medical treatment or dietary change as none, moderate, reasonable, or good. In cases in which a reasonable or good outcome was achieved, owners were asked whether this outcome was the result of diminished frequency, shorter duration of episodes, less severe clinical signs during the episodes, or some combination of these.

Most questions had an “open” answer or a “do not know” option after a list of possible answers in both questionnaires. Furthermore, at the end of both questionnaires, respondents were offered the possibility to give additional comments.

The Dutch questionnaire was distributed to 135 owners of suspected affected Border Terriers from western Europe (the Netherlands and Germany). Suspected cases were recruited through the Dutch Border Terrier Club and private veterinary practitioners. Twenty-five western European Border Terriers were referred to the Utrecht University Clinic for Companion Animals in the Netherlands, and the survey was conducted personally during the visit to the clinic. The questionnaire also could be downloaded from several relevant Internet sites. Owners of Border Terriers with episodic abnormal movements or altered muscle tone were invited to complete the online questionnaire. If answers in returned questionnaires were ambiguous, the responder was contacted by phone for clarification. The Finnish questionnaires were collected following a similar procedure. Seventy Finnish questionnaires were distributed to owners of possible cases, recruited through the Breed Club and veterinary practitioners.

Inclusion Criteria

Border Terriers were regarded as affected if they had experienced ≥3 distinct episodes of abnormal movements or muscle tone (e.g., rigid extended limbs, back or neck, involuntary movements, incoordination, or falling over) at least 2 weeks apart. Dogs with a possible underlying cause (e.g., head trauma, intoxication, heart disease) or neurological abnormalities between episodes were excluded from the study.

The PD questionnaires from Border Terriers that met inclusion criteria were used for statistical analysis of PD characteristics.

Clinical Studies

Twenty-five western European and 10 Finnish Border Terriers that met the inclusion criteria underwent general physical and neurological examinations and blood testing (CBC and biochemical profile including potassium, sodium, calcium, phosphate, glucose, urea, creatinine, alkaline phosphatase, alanine aminotransferase, creatine kinase, total protein, and albumin) at the Neurology Departments of the Companion Animal Clinics of the Universities of Utrecht, the Netherlands and Helsinki, Finland. Additionally, in the Finnish dogs, blood concentrations of triglycerides and cholesterol were determined. In the western European patients, fasting serum bile acid and ammonia concentrations also were measured. Video recordings of episodes were available for 17 (17/25) Border Terriers from western Europe.

Magnetic resonance imaging (MRI) of the brain was performed in 7 western European affected Border Terriers (7/25) with an open magnet 0.2-Tesla magnetic resonance unit with dogs in sternal recumbency. Transverse T1-weighted, T2-weighted, and proton density-weighted studies were obtained. After IV administration of 0.2 mL/kg contrast medium transverse T1, T1 FLASH 3D, subtraction, and dorsal FLAIR series also were acquired.
Magnetic resonance imaging of the neurocranium of 3 (3/10) affected Finnish Border Terriers was made with a 1.5 Tesla MRI system (transverse and dorsal T2-weighted images and T1-weighted 3D images before and after IV administration of 0.1 mmol/kg contrast medium). Additionally, multiplanar reconstructions (MPR) in the sagittal, transverse, and dorsal planes were examined.

In the other 7 affected Finnish Border Terriers (7/10), contrast-enhanced computed tomography (CT) scans of the brain were made. Imaging was performed with a helical dual slice CT scanner. Images in 3 mm slice thickness were obtained before and after administration of 2 mL/kg IV iodinated contrast medium.

Electroencephalography was performed between episodes in all examined affected Finnish Border Terriers (10/10) under medetomidine sedation (0.04 mg/kg). Dogs that resisted needle placement after 15 minutes of initial sedation received an additional dose of medetomidine (0.02 mg/kg). Dogs were placed in sternal recumbency, and SC needle electrodes were inserted over the parietal area. A 17-channel reference montage (F7, F3, Fz, F4, F8, T3, C3, Cz, C4, T4, T5, P3, Pz, P4, T6, O1, O2; reference, on the nose; ground, caudal to the external occipital protuberance). The total recording time was 20 minutes. Each EEG recording was examined visually by an European College of Veterinary Neurology board-certified veterinary neurologist. Additionally, an experienced neurophysiologist evaluated the EEG data. Spikes and sharp waves as well as focal abnormalities of the background were registered. Evaluation of EEG recordings was not blinded.

Seven healthy control Finnish Border Terriers, recruited through the breed club and private veterinary practitioners, underwent the same diagnostic tests.

**Pedigree Analysis**

To identify families with a high prevalence and clarify a possible mode of inheritance, pedigrees of western European cases were analyzed and combined when cases were related to other cases by shared parents, grandparents, or great-grandparents. Pedigree data of dogs participating in our research were used along with data obtained from the Dutch Border Terrier Club and from the Dutch Kennel Club to yield an extensive pedigree of approximately 350 Border Terriers going back 9 generations.

Information about the phenotype of the first 3 generations was scarce. Breeders and owners were able to give information about the phenotype of most of the dogs of recent generations. The phenotype of 134 dogs was established from the questionnaires on PD. A similar pedigree was constructed for the affected Finnish dogs.

**Genetic Studies**

For the genetic studies, inclusion criteria for cases were refined to select "typical cramping cases" based on results of the PD questionnaires: Border Terriers were categorized as affected if they had gone through ≥3 distinct episodes of involuntary abnormal movements, altered muscle tone or both in their lifetime. Consciousness had to be preserved during episodes and dystonia had to be a prominent feature. Onset of the first episode had to be between 1 and 5 years of age, and episodes were considered distinct when they occurred at least 2 weeks apart.

Owners of Border Terriers that met the strict inclusion criteria for "typical cases" based on the results of the PD questionnaires were asked to submit a blood sample from their dog for the genetic studies.

Border Terriers were scored as unaffected if they were ≥7 years of age, and no episodes of abnormal movements or behavior had ever been observed. Unaffected Border Terriers were recruited through the Breed Clubs and private veterinary practitioners. Blood samples from dogs that fulfilled the inclusion criteria and unaffected control Border Terriers were collected with the owners’ consent by veterinarians. The study was approved by the Utrecht University Animal Experiments Committee as required under Dutch legislation (Experiments on Animals Act Wod. 2014, European Directive 2010/63/EU) and the Animal Ethics Committee at the State Provincial Office of Southern Finland (permit: ESAVI/6054/04.10.03/2012). Genomic DNA was extracted from whole blood or buccal swabs with QIAamp DNA Blood Midi Kit (QIAGEN), or salt extraction.17 A genomewide association study (GWAS) was performed using 110 cases and 128 controls from the Border Terrier breed with the Illumina CanineHD BeadChip array containing over 170,000 single nucleotide polymorphisms (SNPs). The genotyped dogs originated from the western European (82 cases, 73 controls) and the Finnish (28 cases, 55 controls) populations.

The SNPs passed quality control when the genotyping rate was >90%, and the minimum allele frequency was >0.1. Individual dogs had to be genotyped at >95% of the SNPs. The level of population stratification was assessed with GenABEL software generating a multidimensional scaling plot of principal components of the DNA data of individual cases and controls. Allele frequency differences between the groups of cases and controls were evaluated in R statistics package 3.0.2 with GenABEL. Population stratification and cryptic relatedness in the sample were adjusted for by mixed model analysis with genomic control implemented in the function mmscore in GenABEL. A correction for multiple testing consisted of 100,000 permutations of the phenotypes of the sample.

Inbreeding coefficients were calculated for all cases and controls with observed and expected numbers of homozygous genotypes, based on the population of origin, by PLINK. To analyze whether inbreeding coefficients were significantly different between cases and controls, a Student’s t-test was performed using Microsoft Excel.

**Results**

**Prevalence Study**

At the request of the Dutch Border Terrier club, 2 cohort studies on general characteristics, behavior, and the prevalence of several health problems, including neurological disorders, were conducted. In 2004, 670 of 1,126 (60%) and in 2009 918 of 1,494 (61%) questionnaires were completed and returned. In 2004, episodes with abnormal movements or posture were most common with a prevalence of 7.6% in Border Terriers born between 1998 and 2001. Five years later, the reported prevalence of such episodes in Border Terriers born between 2003 and 2006 was 4.8%.

**Questionnaire on PD**

One-hundred fifty-eight copies of the Dutch questionnaire were completed and returned. One-hundred seven of those returned, 56 males (17 neutered) and 61 females (49 neutered), met the inclusion criteria for the affected state. Ninety-six of the included dogs were Dutch and 4 came from Germany. Additionally, questionnaires about affected Border Terriers from Belgium (3), the United Kingdom (3), and Switzerland (1) that were completed online also were included. The
population from these countries together is referred to as the western European population.

In the Finnish survey, 56 questionnaires were completed, and 40 dogs, 19 females (8 neutered) and 21 males (4 neutered), fulfilled the inclusion criteria.

The median age of onset of clinical signs was 2 years in the western European dogs and 3 years in the Finnish dogs (range, respectively, from 3 months to 9 years and from 6 months to 9 years). Of the western European dogs, 8% had episodes every 6 weeks, 4% every 4–5 months, and 9% every 1–2 years. Of the Finnish dogs, 9% had episodes every 2–3 weeks, 6% every 4–5 weeks, and 8% every 6–7 weeks. The majority of dogs (57%) had an episode frequency of less than once every 7 weeks. The median number of episodes in the Finnish population was 7 per year. The yearly number ranged from 1 to approximately 200 in both populations.

The majority of Finnish owners (58%) noticed that their dogs were prone to episodes in particular situations or emotional states, whereas 40% of the western European owners observed predisposing factors. Typical situations or emotional states preceding episodes included physical exercise (20%), stress (16%), heat (7%), hot weather (5%), and loud noise or bright lights (3%). Conversely, 16% of owners of affected Border Terriers reported that episodes usually occurred during rest or sleep.

Of the western European and Finnish owners, respectively, 59% and 44%, noticed signs preceding the episodes in their dogs. The most typical signs were attention seeking and restlessness in both groups. Other signs before the episodes included withdrawal, a stiff gait, freezing (ie, stiffening and not moving), absence of consciousness, staring, panting, fear, perceived nausea, vomiting, and salivating. The duration of the phase with these signs varied markedly between 30 second and 48 hour (median, 5 minutes, with the above-mentioned signs varied markedly between 1 minute and 48 hour (median, 5 minutes).

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was not available, but the diet was considered unlikely to be gluten-free, because most owners combined several foods. All dogs receiving hypoallergenic diets showed reasonable (40%, 6/15) or good (60%, 9/15) improvement of clinical signs after dietary change.

**Clinical Studies**

General physical examination and neurological examination identified no clinically relevant abnormalities in all 35 affected dogs examined, nor in the 7 healthy controls. One affected dog showed slightly decreased postural reactions in the right pelvic limb, which was considered to be an unrelated problem. Complete blood count and biochemical profile results were within reference intervals except for some slight and inconsistent abnormalities in both groups. Alkaline phosphatase activity was mildly increased (highest activity 257 U/L) in 5 of 35 affected dogs. However, 3 of them had been treated with phenobarbital, a drug known to increase total alkaline phosphatase activity. All of them had fasting serum bile acid and ammonia concentrations within reference intervals.

Magnetic resonance or CT imaging of the brains of 17 affected Border Terriers and 7 healthy controls was unremarkable. No abnormal activity was detected on EEGs recorded between episodes in 10 affected and 7 healthy control Border Terriers.

**Pedigree Analysis**

Inspection of pedigrees of affected western European and Finnish Border Terriers showed a high prevalence of cases in specific lines, whereas other lines were free of disease. Most cases had healthy parents and, in approximately half of the affected litters, >1 individual was affected (Figs 1 and S1). Because the health status of a large number of parents and siblings of affected dogs could not be confirmed, we could not perform segregation analysis to determine the most likely mode of inheritance.

**Genetic Studies**

We performed a GWAS with 238 ascertained cases and controls to detect chromosome regions that could harbor genes involved in PD. A total of 104,079 SNPs passed quality control. The multidimensional scaling plot showed an even distribution of cases and controls in the sample, indicating that there were no large differences in the genetic background of the case and control groups (Fig 2). However, the genomic inflation factor was found to be high ($\lambda = 1.8$), meaning that marker alleles were in general not distributed evenly over the dogs in the sample as a consequence of population stratification. The results were corrected for this.
inflation factor. No chromosome regions with significant association to the disorder were observed. A cluster analysis whereby the sample was divided into geographic subgroups did not alter this result. A weak association, after correcting for data stratification and multiple testing by a permutation procedure, was found on chromosome 2 (BICF2P455713; \( P = .24 \), Fig 3). Notably, no association whatsoever with the regions of the genome containing genes related to PDs in humans (PNKD, KCNMA1, PRRT2 and SLC2A1) was detected.

Mean inbreeding coefficients (±SD) were 0.034 ± 0.097 and 0.012 ± 0.061 for cases and controls, respectively. A Student’s t-test was performed and indicated that the difference between cases and controls was significant (\( P = .042 \)).

**Discussion**

Epidemiological, clinical, and genetic studies of dogs with epilepsy and episodic movement disorders are hampered by difficulty in correctly diagnosing and classifying them. Because neurological examination between episodes usually is normal, the clinician or researcher is reliant primarily on the descriptions of attacks by owners, who may be biased or may misinterpret signs. Attacks may not be recognized or may be missed during the night or in the absence of the owner. Furthermore, even for an experienced neurologist, it can be difficult to differentiate among atypical focal epileptic seizures, paroxysmal dyskinesias, and other paroxysmal disorders without further diagnostics such as ictal EEG recordings.

Another challenge in describing a newly recognized syndrome with variable phenotype is to assess whether less common signs are part of the phenotypic variation or represent another disorder of independent etiology. Hence, formulating inclusion and exclusion criteria can be difficult, and one should be careful to avoid circular reasoning. For example, in 1 study dogs that displayed autonomic signs such as urination, defecation, and salivation during episodes were excluded beforehand.\(^\text{16}\) Subsequently, in the discussion, it was concluded that these autonomic signs were consistently absent in CECS, which was used as an argument against crampind episodes being an epileptic disorder. Border Terriers with other autonomic signs such as borborygmi or vomiting related to the episodes were not excluded.

Here, we used broad inclusion criteria for enrollment in the PD questionnaire study, and characteristic signs were defined afterward based on the results. Therefore, we cannot rule out the possibility that some dogs initially included suffered from other disorders such as idiopathic epilepsy. However, most exhibited a phenotype that was distinctly different from that of typical idiopathic epilepsy (eg, only 2% of the western European owners reported loss of consciousness during episodes). For the genetic studies, inclusion criteria were refined based on the outcome of the questionnaires to select the most typical cases.

Clinical characteristics reported in the western European and Finnish populations of Border Terriers with PD generally were comparable. The episodes’ phenomenology, severity of signs, and frequency of episodes, however, varied considerably among individual dogs. However, consciousness was consistently unimpaired during the episodes in most cases. Results of clinical examinations, blood testing, and diagnostic imaging generally were unremarkable.

The clinical features reported here are mostly similar to those described previously in smaller groups of German and British Border Terriers.\(^\text{16,23}\) Therefore, we conclude that these populations most likely suffer from the same condition. Recently, comparable syndromes have been described in Norwich Terriers\(^\text{24}\) and in a young Yorkshire Terrier.\(^\text{25}\)

It has been postulated that the CECS phenotype is suggestive of PD rather than focal epilepsy.\(^\text{16}\) The combination of preserved consciousness and dystonia of all limbs during episodes as encountered in many affected Border Terriers is a strong indication for this distinction. In addition, epileptic seizures in dogs usually are brief (most last <3 minutes\(^\text{26}\) ), whereas episodes of PD often last >5 minutes and episodes of >2 hours were reported.

The lack of abnormalities on EEG recordings between episodes in our study strongly supports the diagnosis of PD. Abnormal interictal activity on EEG recordings has been identified in 25–65% of dogs with a clinically established diagnosis of epilepsy,\(^\text{27–29}\) whereas an abnormal EEG is rare in PDs.\(^\text{8}\) In our study, none of the 10 affected Border Terriers that were investigated using EEG between episodes had abnormal EEG recordings, making epilepsy unlikely. Unfortunately, we were not able to perform EEG recordings during episodes, and thus confirm with greater certainty that the episodes were not epileptic seizures.
The presence of a phase with clinical signs directly after the episodes in the majority of affected Border Terriers and autonomic signs in some are less typical for PD as described in humans. Nevertheless, based on the considerations described above, focal epilepsy is less likely and the term CECS can be replaced by the descriptive term PD, which refers to a group of movement disorders characterized by recurrent episodes of hyperkinesia, altered muscle tone, or both.

In humans, PDs are categorized primarily based on precipitating events. Because episodes in Border Terriers are not typically triggered by sudden movement or prolonged exercise, they are most consistent with paroxysmal nonkinesigenic dyskinesia (PNKD).

The debate about the pathophysiology of PD is ongoing, but neurophysiological and functional imaging studies suggest a major role for the basal nuclei and related structures. Some authors suggest that PKD is a form of subcortical epilepsy involving the basal nuclei and their connections. This is further supported by the finding that lesions of the basal nuclei can result in subcortical epilepsy. As in humans treated with primidone, no abnormalities were detected in the region of the basal nuclei during diagnostic imaging of the brains of affected Border Terriers.

In contrast to previous reports, most owners of Border Terriers treated with anti-epileptic drugs, especially phenobarbital and diazepam, judged the therapy to be beneficial. In other reports, the different efficacy of these protocols used make it difficult to draw meaningful conclusions. Furthermore, a substantial placebo effect, manifested as a decrease in seizure frequency, has been identified in epilepsy treatment trials in dogs. This probably also is applicable to other paroxysmal disorders. Consequently, to evaluate the efficacy of medical treatment on PD in Border Terriers, prospective double-blind placebo-controlled studies are required.

A beneficial effect of anticonvulsant therapy also has been reported in PD in humans. Especially, PKD responds dramatically to anti-epileptic drugs, even at low dosages. In PNKD, a favorable response to benzodiazepines is observed in some cases. An episodic movement disorder in a German Shorthaired Pointer responded well to low dosages of both phenobarbital and potassium bromide.

Most owners who changed the diets of their affected Border Terriers stated that doing so resulted in reasonable to good improvement of clinical signs. In dogs that were changed to a commercial hypoallergenic diet (in all cases gluten-free), a reasonable to good effect was noted in all cases. A favorable effect of dietary change also was observed in another study. Although the above-mentioned placebo effect might have resulted in overestimating the beneficial effect of the hypoallergenic diet, there are strong indications that diet influences the clinical course of the disease.

In human medicine, neurological manifestations including cerebellar ataxia, myoclonus, chorea, and epilepsy have been reported in 22.5–51% of patients with celiac disease (CD). Celiac disease is a multisystem immune-mediated disorder triggered by the ingestion of gluten, predominantly causing gastrointestinal clinical signs. However, neurological signs without enteropathy are increasingly recognized. Genetic factors play an important role in the development of CD. A girl with confirmed CD and a movement disorder resembling PNKD has been reported. Neurological clinical signs completely resolved after introduction of a gluten-free diet. Recently, increased concentrations of antitransglutaminase and antigliadin antibodies were identified in the serum of 6 Border Terriers with CECS. A strict gluten-free diet resulted in clinical and serological improvement in all dogs. It was concluded that CECS in Border Terriers is a gluten-sensitive condition, triggered and perpetuated by gluten.

It seems plausible that the significantly higher inbreeding coefficients in PD cases compared to controls observed in our study reflect an underlying genetic cause. Additionally, pedigree analysis identified an increased prevalence of affected dogs in specific families of Border Terriers. Together with the observation that PD occurs almost exclusively in Border Terriers, these findings support a complex mode of inheritance. Addi-

The selection for dog breeds in the past few centuries resulted in a unique population structure, with high levels of genetic homogeneity within breeds. This situation greatly facilitates studies that attempt to unravel the genetic background of inherited diseases. Genomewide association studies aim to identify genetic markers that are associated with a specific phenotype in a family or a population. GWAS is a powerful tool to identify loci of monogenic traits in relatively small numbers of cases and controls. For instance, a GWAS of 5 cases and 8 controls sufficed to localize the gene for episodic falling syndrome in Cavalier King Charles Spaniels. Another GWAS of 23 cases and 37 controls effectively mapped the gene for disproportionate dwarfism in Labrador retrievers. According to a study of modeling in dogs, the power of our GWAS to detect a locus with dominant inheritance was at least 99%, whereas the power to detect a locus that multiplies the relative risk of the phenotype by 5-40% was 97%.

Failure to achieve conclusive results in a GWAS of a cohort of 110 cases and 128 controls with a large informative set of SNPs suggests that inheritance of PD in Border Terriers likely is complex. Furthermore, the marked variety in clinical presentation among cases further supports a complex mode of inheritance. Additional studies to elucidate the genetic background are required and could involve whole genome sequencing in well-characterized pedigree samples.

In conclusion, the presented survey and EEG studies provide further evidence that the studied syndrome in Border Terriers is a PD rather than epilepsy. Our genetic studies suggest that PD probably is a disorder with complex inheritance.

Footnotes

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Acknowledgments

We thank members of the “Nederlandse Border Terrier Club” and the “Border Terrier Club of Finland” for their cooperation. Furthermore, we are grateful to all breeders and owners of Border Terriers who donated blood samples, completed questionnaires or both. We thank Ranja Eklund, Minna Virta, Sini Karjalainen, Reetta Hänninen, and Aino Pentikäinen for technical assistance. Dr. Valerie Jonckheer-Sheehy is gratefully acknowledged for editing the manuscript.

Conflict of Interest Declaration: Authors declare no conflict of interest.

Off-label Antimicrobial Declaration: Authors declare no off-label use of antimicrobials.

References


Supporting Information

Additional Supporting Information may be found online in the supporting information tab for this article:

Figure S1. Pedigree of Finnish Border Terriers segregating PD. Black symbols: affected; unfilled symbols: unaffected. Squares: males; circles: females.