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Hereditary Cerebellar Degeneration in Scottish Terriers

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Background: Hereditary cerebellar degeneration is described in several dog breeds. This heterogeneous group of diseases causes cerebellar ataxia associated with cerebellar cortical degeneration.

Objective: To report the clinical and histopathological features, and describe the mode of inheritance of hereditary cerebellar degeneration in Scottish Terriers.

Animals: Sixty-two affected dogs recruited through the Scottish Terrier Club of America.

Materials and Methods: *Prospective, observational study*: Owners of affected dogs were contacted for a description of clinical signs, age of onset, and disease progression. Medical records, videotapes of gait, and brain imaging were evaluated. When possible, necropsy was performed and the brain examined histopathologically. Prevalence of the disease was estimated and a pedigree analysis was performed to determine mode of inheritance.

Results: Gait abnormalities were noted in the 1st year of life in 76% of dogs, and progressed slowly; only 1 of 27 dogs dead at time of writing was euthanized because of cerebellar degeneration. Clinical signs included wide based stance, dysmetria, intention tremor, and difficulty negotiating stairs and running. Cerebellar atrophy was detected on magnetic resonance imaging. On histopathological examination, there was segmental loss of Purkinje neurons, thinning of molecular and granular layers, and polyglucosan bodies in the molecular layer. Prevalence of disease was estimated at 1 in 1,335 American Kennel Club registered Scottish Terriers. Genetic analysis results are consistent with an autosomal recessive mode of inheritance.

Conclusion and Clinical Importance: A hereditary cerebellar degenerative disorder with a relatively mild phenotype has emerged in the Scottish Terrier. Genetic studies are needed.

Key words: Canine; Cerebellar abiotrophy; Cerebellar ataxia; Polyglucosan body; Purkinje cell.

Hereditary degenerative cerebellar disorders are an important problem in purebred dogs. The most commonly recognized categorizes of this type of condition are abiotrophies (cell death is believed to be due to an intrinsic metabolic disorder)[1] and lysosomal storage diseases.[2] The cerebellar cortex is the primary site of neurodegeneration and in the most common form, there is severe loss of Purkinje cells associated with a depletion of granule cells and atrophy of the molecular layer.[1] This has been reported in a wide range of breeds.[1–22] In another form, granular cell loss is the primary event, with relative sparing of Purkinje cells.[3–7] Progressive neuronal loss causes the development of a mixture of cerebellar and central vestibular signs, including a dysmetric gait, loss of balance, a wide-base stance, and intention tremors. Age of onset and progression varies between breeds and individuals. When a hereditary basis has been established, the most common mode of inheritance is autosomal recessive.[1,3,8,12–14,16,20]

Abbreviations:

AKC	American Kennel Club
CSF	cerebrospinal fluid
GFAP	glial fibrillary acidic protein
LFB	luxol fast blue
MRI	magnetic resonance images
NCSU	North Carolina State University
PAS	periodic acid-Schiff
SD	standard deviation
SCAs	spinocerebellar ataxias

A case report of a Scottish Terrier describing cerebellar cortical degeneration was published in 2001.[21] Subsequent to this report, cerebellar cortical degeneration has emerged as an important problem in the Scottish Terrier breed, leading us to collect clinical information on a large number of affected dogs. The purpose of this paper is to report the clinical and histopathological features of hereditary cerebellar cortical degeneration in a group of Scottish Terriers, and to describe the mode of inheritance of the disease in this breed.

Materials and Methods

Affected Scottish Terriers were recruited through the Scottish Terrier Club of America. Owners were contacted by telephone and detailed descriptions of the history and clinical signs were obtained. Medical records and videotapes of gait when walking, running, and negotiating steps were evaluated when available. When performed, copies of magnetic resonance images (MRI) of the brain and results of cerebrospinal fluid (CSF) analysis were reviewed. The progress of each dog was followed every 3 months by e-mail or telephone communication with the owner from the time of inclusion in the study in order to map each dog's clinical course.

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Diagnosis was confirmed by postmortem examination of the brain when dogs were euthanized. Dogs that were euthanized at university veterinary schools underwent a complete postmortem examination, but if euthanized elsewhere, the brains were removed, placed in 10% buffered formalin, and shipped to North Carolina State University (NCSU) for histopathological examination. After fixation, the brains were sectioned and embedded in paraffin using routine techniques. Six-micrometer sections were cut and stained with hematoxylin and eosin. In addition, sections from brains that were evaluated at NCSU were stained with luxol fast blue (LFB) in order to evaluate myelin, Bielschowsky silver stain to evaluate axons, periodic acid-Schiff (PAS) to detect carbohydrates, and Sudan Black to detect lipids. Immunohistochemical staining for glial fibrillary acidic protein (GFAP) was performed to evaluate astrocytes using routine techniques. The brain of a neurologically normal 11-year-old Scottish Terrier was evaluated in the same way to provide a normal reference.

Based on evaluation of the medical records, videotapes, and conversations with the owners, affected dogs were grouped into 4 categories to reflect the criteria by which the diagnosis was made. In category 1, the diagnosis was confirmed by necropsy. Dogs in category 2 had undergone a complete diagnostic workup with MRI of the brain, with or without CSF analysis. In category 3, the dogs showed neurological signs and history consistent with cerebellar degeneration and were related within 3 generations to one of the dogs in categories 1 or 2, and in the last category, dogs had consistent neurological signs and history.

Pedigrees of the affected dogs and details of their littermates and parents were obtained when available. Litter analysis of the dogs in categories 1 and 2 was performed to determine the mode of inheritance. In order to estimate the minimum prevalence of the disease, the number of Scottish Terriers registered with the American Kennel Club (AKC) from 1994 to 2004 was compared with the number of known affected AKC registered dogs that were born in those years.

Results

Sixty-two affected dogs were identified from Australia (n = 2), Canada (n = 5), Japan (n = 1), the United Kingdom (n = 1), and the United States (n = 53). Twenty-five dogs were female, and 37 were male. Twenty-seven dogs were dead at the time of writing. The diagnosis was confirmed in 10 of these dogs by histopathology, one of which was also examined by MRI (category 1). Four dogs underwent an MRI of the brain without histopathology (category 2). There were 24 dogs in the 3rd category, and 24 dogs were placed in category 4. CSF analysis was performed in one of these dogs. The dogs were followed for a mean of 1.5 years (range 6 months to 4 years) at the time of writing.

Twenty-one dogs were adopted when adult and their previous clinical history was therefore unknown. Age of onset of gait abnormalities reported by owners of the remaining 41 dogs ranged from 2 months to 6 years (median: 7 months). In the majority of dogs (31 of 41 dogs, 76%), onset of signs was noted during the 1st year of life. Two owners reported that their dogs were clumsy from birth. The 1st sign noted by owners was a gait abnormality of the pelvic limbs. Affected dogs initially appeared normal when walking in a straight line, but when running or walking slowly up and down stairs, hind limb ataxia became evident. As the disease progressed, owners reported that dogs developed noticeable gait abnormalities in all 4 limbs, and they described hypermetria of the thoracic limbs. It became progressively more difficult for the dogs to negotiate stairs and they lost control of their pelvic limbs when running. Owners described this as bunny hopping and the pelvic limbs moving faster than the thoracic limbs, resulting in somersaulting and falling. An intention tremor was noted in 12 dogs. Thirty-four owners reported slow changes of signs over a period of years (median: 6 years; range 1–12 years; SD: 2.76). Twelve owners reported that their dogs had no further clinical deterioration after initial onset of signs. This stabilization of signs occurred at 1 year of age (range: 1–3; SD: 0.79). These dogs maintained stable signs (with mild or moderate signs) for a median of 6 years (range: 1–11 years; SD: 3.41). One owner reported that their dog's signs became severe over a period of 2 years. We were unable to maintain contact with 15 owners and could not establish progression in these dogs.

Videotapes of 53 dogs were reviewed. The remaining 9 dogs were not videotaped but the diagnosis was confirmed in 5 of these dogs by necropsy and 2 by MRI. The remaining 2 had consistent neurological signs and history and were related to dogs in category 1 and 2. Based on review of the videotapes and neurological history, affected dogs exhibited classic signs of cerebellar disease characterized by a wide-based stance, ataxia of all 4 limbs with hypermetria more obvious in the thoracic limbs, and difficulty negotiating stairs causing stumbling and falling. Six of the dogs had an intention tremor visible on the videos and 1 dog was visual, but had absent menace responses (reported by the neurologist who examined him). Eleven dogs had mild signs (hypermetria of all 4 limbs when walking that was more evident when running or negotiating steps but did not affect the dogs' activity level). These dogs ranged in age from 1 to 11 years (median: 6 years). In 35 dogs the signs of ataxia were more severe and were affecting the dogs' activity level. These dogs bunny hopped and somersaulted dramatically when running and made frequent errors when negotiating steps. These moderately affected dogs ranged in age from 1 to 14 years (median: 7 years). Eleven dogs, ranging in age from 2 to 13 years (median: 11 years), had severe signs, making it difficult for them to walk. One of these dogs crawled with its neck extended close to the ground and its thoracic limbs rose above the head during limb protraction. There was information on age and reason for euthanasia in 24 of the 27 dogs that were dead. The age of euthanasia ranged from 20 months to 15 years (median: 10 years). Only one of the affected dogs was euthanized because of cerebellar degeneration at the age of 12 years. All the other dogs were euthanized for a variety of unrelated disorders.

Cerebellar atrophy was evident on MRI of the brain in 5 dogs. There was increased space between the folia that was most clearly detected on T2-weighted sagittal images. The atrophy was more obvious in the dorsal half of the cerebellum (Fig 1).

On gross examination of the brain following euthanasia, the overall size of the cerebellum appeared small although the severity of changes varied between dogs (Fig 2). Histologically, extensive degeneration of the cerebellar cortex was associated with segmental loss of Purkinje neurons, which was nearly complete in some folia. This

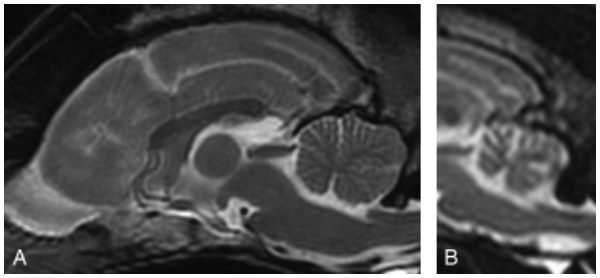

Fig 1. T2-weighted mid-sagittal MRI of a mildly affected 1-year-old Scottish Terrier (**A**) and a severely affected 11-year-old Scottish Terrier (**B**). There is increased cerebrospinal fluid (hyperintense signal) between the cerebellar folia in the rostral dorsal region of the cerebellum in A and throughout the cerebellum in B.

was accompanied by marked atrophy of molecular and granular layers. Changes were pronounced dorsally throughout the cerebellum, but were less severe ventrally, even in severely affected dogs. In particular, the nodulus and uvula appeared relatively spared. Changes were more severe at the apical tips of the folia in moderately affected areas. In regions with severe changes, the borders between the cerebellar cortical layers became blurred, granular neurons became loosely spaced, and frequently, spared Golgi neurons were visible in the granular layer (Fig 3). This loss of organization and mild gliosis resulted in increased cellularity of the junction between the granular and molecular layers. Bielschowsky stains highlighted significant reorganization of the neuronal endings on Purkinje neurons following death of the Purkinje neuron. The normal basket like appearance of nerves around the Purkinje neurons was lost in severely affected regions (Fig 4). Staining with PAS, LFB, and Bielschowsky revealed intensely staining circular bodies within the molecular layer. These inclusions were also present in the age-matched control Scottish Terrier and an age-matched American Staffordshire Terrier but at lower frequency. Some Purkinje neurons also contained small amounts of PAS positive material (Fig 5). Staining with Sudan Black did not reveal abnormal storage of lipid anywhere in the brain. GFAP immunohistochemistry showed mild astrogliosis in the regions of Purkinje neuron loss. There was no evidence of involvement of the cerebellar nuclei or other regions of the brain.

Fifty-three of the 62 affected dogs had a known pedigree. Based on interviews with breeders and owners, 27 affected dogs had 2 phenotypically normal parents, and 1 affected dog had an affected mother and a normal father. Parental phenotype could not be confirmed in the other affected dogs. Five pairs and 1 trio of affected dogs

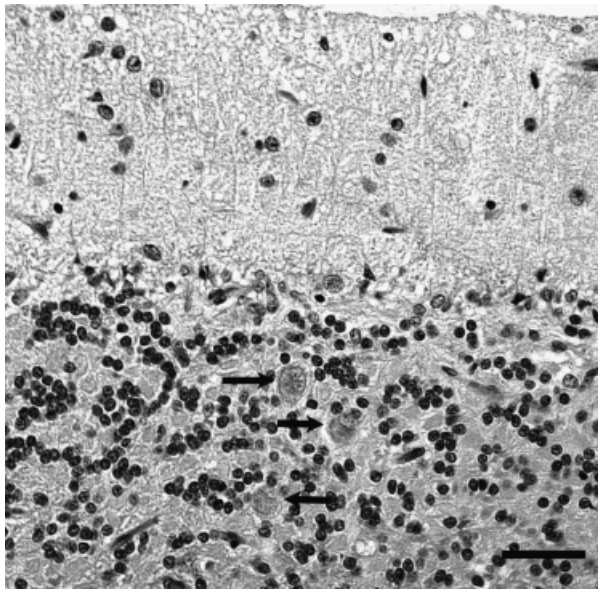

Fig 3. The cerebellar cortex of an affected 12-year-old Scottish Terrier (hematoxylin and eosin). There is complete loss of Purkinje neurons between the molecular and granular layers. Spared Golgi neurons are visible in granular layer (arrow). There is a thinning of molecular and granular layers. Bar = 50 μM.

were full siblings. Two affected dogs were half siblings to other affected dogs and the remaining dogs for which information was available were single affected dogs. Litter analysis was possible on 11 of the 14 category 1 and 2 dogs. The remaining 3 had unknown parentage (2) or litter information was not available (1). Litter analysis showed 12 affected dogs out of 49 (24.5%) total offspring in 11 litters from phenotypically normal parents. Using Lenz-Hogben correction for bias of ascertainment, Chi-squared analysis confirmed that the litter analysis was consistent with a fully penetrant simple autosomal recessive mode of inheritance ($\chi^2 = 1.16$, $df = 1$, $P = .2045$). A pedigree map of 44 of the 53 affected Scottish Terriers with pedigrees (Fig 6) shows the breadth of pedigree involvement of the defective gene, including United States, Canadian, and Australian registered dogs. The common ancestors of all affected dogs go back to British registered dogs from the 1960s. A total of 50,720 Scottish Terriers were registered with the AKC from 1994 to 2004 and 38 affected dogs registered with the AKC were born in the same period. The minimum prevalence of the disease in the registered population of Scottish Terriers was estimated at 1 in 1,335 dogs.

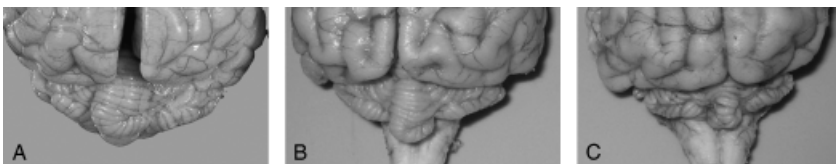

Fig 2. Images of the dorsal surface of the cerebellum from a normal 2-year-old Beagle (**A**), a moderately affected 9-year-old Scottish Terrier (**B**), and more severely affected 12-year-old Scottish Terrier (**C**). The atrophy of the cerebellar vermis and hemispheres is clearly evident in images B and C.

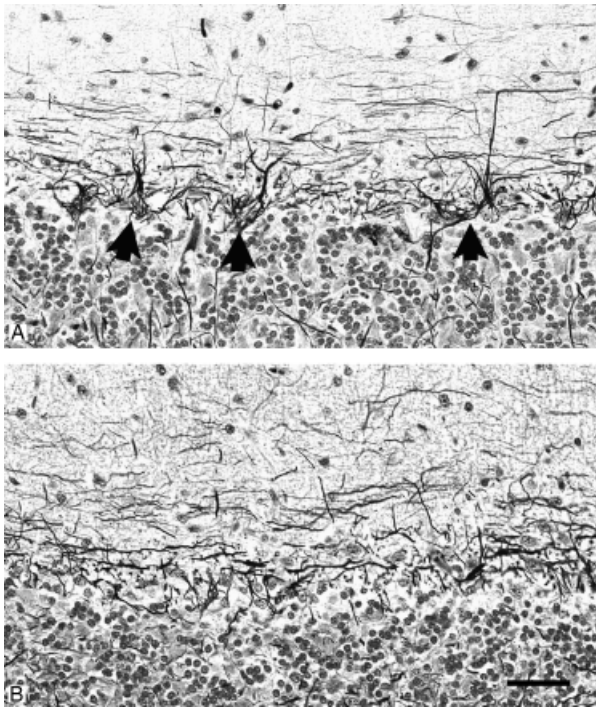

Fig 4. The cerebellar cortex of an affected 12-year-old Scottish Terrier (Bielschowsky). In some regions, the basket cells can still be seen although Purkinje neurons have died (arrow) (**A**). In a different region of the same dog, there has been extensive remodeling and the basket-like arrangement has been lost (**B**). Bar = 50 μM.

Discussion

Scottish Terriers suffer from a hereditary cerebellar cortical degenerative disorder in which the age of onset of clinical signs is variable but occurs most commonly in the 1st year of life. In the majority of dogs these clinical signs progress slowly over many years. This group of neurodegenerative disorders is relatively common in purebred dogs, but each breed appears to have a different phenotype with respect to the range of signs shown, age of onset, and rate of progression,[3,12–14,16,20,22] suggesting different genetic etiologies in different breeds. Information from a relatively large group (62 dogs) of affected Scottish Terriers was compiled for this report. However, definitive diagnosis based on histopathology was only established in 10 dogs. The 28 dogs in categories 2 and 3 are unlikely to be misdiagnosed, but the diagnosis was based on clinical signs and histories only in the remaining 24 dogs. The owners of these dogs declined advanced imaging of their dogs' brains but were willing to keep in close contact to allow us to monitor their dogs' signs. All dogs in this group have exhibited signs for >6 months and it is unlikely that these dogs are suffering from an infectious, neoplastic, or congenital disorder given the slowly progressive nature of their signs. During the course of this study, the diagnosis was confirmed in every case that was euthanized and underwent a necropsy, in support of the clinical diagnosis.

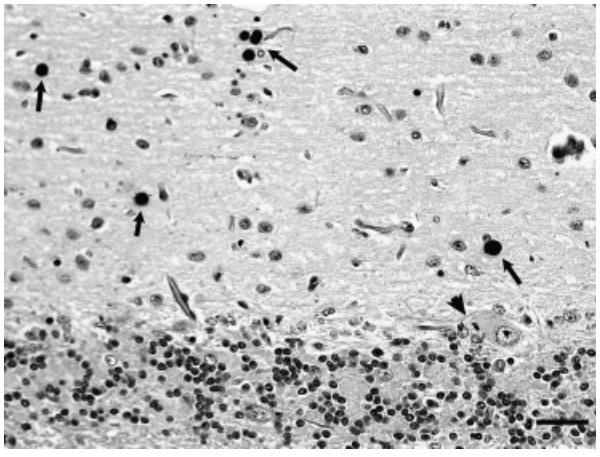

Fig 5. Periodic acid-Schiff (PAS) staining of the cerebellar cortex of an affected 12-year-old Scottish Terrier. Circular PAS positive inclusions can be seen in the molecular layer (arrow). There is positive PAS material in Purkinje neuron (arrow head). Bar = 50 μM.

When compared with other breeds, cerebellar degeneration in Scottish Terriers is similar to the disorders described in Gordon Setters and Old English Sheepdogs (onset of signs between 6 and 40 months of age with a slow rate of progression).[13,16] The clinical manifestations of cerebellar degeneration in Scottish Terriers include classic cerebellar signs of hypermetric ataxia, spasticity, wide-based stance, balance loss, and intention tremors, the severity of which varied from dog to dog. In the majority of dogs, the owners felt the signs were mild to moderate, and did not greatly impact their mobility or quality of life. However, 11 dogs exhibited a severe phenotype between 2 and 13 years of age. In addition to these classic cerebellar signs, affected Scottish Terriers tend to lose control over their hindquarters when moving at speed, causing somersaulting. This dramatic clinical sign has been reported in other breeds with neurodegenerative disorders, such as American Staffordshire Terriers,[12] Kerry Blue Terriers,[20] and Chinese Cresteds.[22] However, these breeds have a more widespread pathology.[12,20,22]

Scottish terriers also develop another hereditary neurological disorder called Scottie cramp.[23] In this paroxysmal disorder, excitement, fear, or exercise triggers muscle hypertonicity and causes generalized spasticity with the pelvic limbs held over the neck due to flexion of the coxofemoral joints. Unlike dogs with cerebellar degeneration, the signs shown by dogs with Scottie cramp are episodic, and resolve with rest.[23] However, mildly affected dogs with cerebellar degeneration can appear relatively normal until they run. It is therefore possible that cerebellar degeneration has affected the Scottish Terrier breed since the 1st descriptions of Scottie cramp in the 1940s[24] rather than being a new disease. This could explain in part the unexpectedly high estimate of the prevalence of this disease.

The neuropathological abnormalities described in cerebellar degeneration differ between affected breeds but a large number have the common thread of Purkinje cell loss.[25] Histopathologically, the loss of cerebellar cortical neurons was more severe in the dorsal aspect of the cerebellum in the Scottish Terriers (similar to Kerry Blue Terriers[25]) and the uvulus and nodulus were relatively spared. There was only 1 age-matched control brain available, and this "normal" dog's brain did not exhibit the

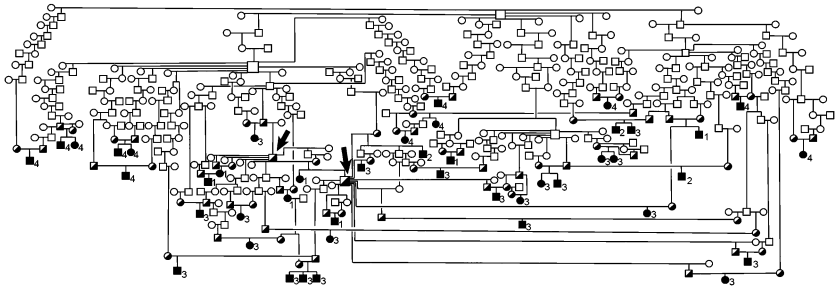

Fig 6. Pedigree map of Scottish Terriers with cerebellar degeneration. Squares are males and circles are females. Solid symbols are affected dogs. Half-filled in symbols are obligate carriers. Unfilled symbols are phenotypically normal or of unknown phenotype. The black arrows indicate the 2 common ancestors that are proven to be carriers by producing affected offspring.

changes noted in the affected dogs. A larger cohort of age and breed-matched controls would be desirable for more detailed comparison of the histopathological changes. Storage disorders commonly cause loss of Purkinje neurons but PAS, LFB, and Sudan Black staining did not consistently reveal accumulations of carbohydrate or lipid within Purkinje neurons. However, these stains did highlight inclusions, usually located deep in the molecular layer. The staining pattern of these inclusions made them most consistent with polyglucosan (Lafora-like) bodies.[26] Polyglucosan bodies can be located in neurons or glia, and are made up of accumulations of abnormal insoluble glycogen.[27] They can be subclassified as Lafora bodies, found at high densities in the brain, heart, liver, muscle, and skin in Lafora disease, a neurodegenerative disease causing progressive, fatal myoclonic epilepsy.[27] They can also be classified as corpora amylacea, found as part of the normal aging process in humans and in dogs,[27] and indeed, we identified them in our control dogs, although at a lower frequency. Lafora disease in humans can be caused by mutations in the *EPM2A* and *EPM2B* gene, encoding laforin and malin proteins, respectively.[28] Laforin and malin play critical roles in the ubiquitin-proteosome system and maintenance of the normal glycogen structure.[28] There are reports of similar inclusions in dogs with myoclonic epilepsy and motor deficits.[29–31] Indeed, Lafora disease in wire-haired dachshunds with myoclonic epilepsy is associated with *EPM2B* mutations.[29] However, in these dogs, polyglucosan bodies were widely distributed at a high density throughout the brain. It is currently unclear whether the polyglucosan bodies identified in Scottish Terriers represent a primary pathological process or a secondary event. More detailed analysis of the pathology will be presented elsewhere.

The mode of inheritance of cerebellar degeneration in Scottish Terriers is consistent with an autosomal recessive gene. At least 4 more affected Scottish Terriers have been identified in South Africa (van der Merwe, personal communication). Their pedigrees trace back to dogs that were imported from the United Kingdom before the 1960s. It is therefore likely that the defective gene causing cerebellar degeneration in Scottish Terriers is old and widespread. The pedigree map shows prolific ancestral males as common ancestors to affected dogs. When prolific males are bred to a diverse pedigree background of females, they become ancestral convergence points in pedigrees. They are the closest common ancestors of affected dogs, but this does not implicate them as carriers. Only 2 ancestral common ancestors are proven to be carriers by producing affected offspring. The computed prevalence of 1 in 1,335 dogs is a minimum estimate based on the identified affected dogs. It is assumed that additional affected dogs exist that have not been brought to the authors' attention. Cerebellar degeneration in the Scottish Terrier is not an uncommon disorder, with several affected dogs born annually worldwide.

The genetic etiology of hereditary cerebellar cortical degeneration in dogs is likely to be diverse. In humans, hereditary or spinocerebellar ataxias (SCAs), neurodegenerative diseases that affect the cerebellum, can be inherited as autosomal dominant, recessive, sex-linked, or mitochondrial traits.[32] Autosomal dominant SCAs are more common than the recessive form in humans, unlike dogs. According to the genetic loci, over 45 different types of SCA have been identified in humans.[32–34] A wide range of different abnormalities ranging from ion chanelopathies, dysfunctional structural proteins, mutated growth factors, and abnormal protein aggregation (trinucleotide expansion) can result in overlapping clinical signs and neuropathological changes.[33] There are numerous other mutations known to cause cerebellar cortical degeneration in rodents.[35,36] One or more of these causes may be found to be the basis of what we now refer to as abiotrophy. The mutation causing cerebellar degeneration in American Staffordshire Terriers is known[b,37] and, while the mutation is still unknown, a linked marker-based genetic test is available for the disease in Italian Spinone (http://www.aht.org.uk/genetics_spinone.html). The large number of potential candidate genes for these diseases means that a full genome screen with linkage or association studies is the most efficient way to identify the causative mutation for this type of disorder in dogs and this work is underway in Scottish Terriers.

Footnotes

[a] Urkasemsin G, Olby NJ, Mehta PM, Bell JS. Hereditary cerebellar cortical degeneration in Scottish Terriers. Presented at the 26th Annual ACVIM Forum, San Antonio, TX, June 4–7, 2008. J Vet Intern Med 2008;22:723 (abstract)

[b] Olby NJ, Harris T, Mehta PM, et al. Linkage analysis in American Staffordshire Terriers with hereditary cerebellar cortical degeneration. Presented at the 25th Annual ACVIM Forum, San Antonio, TX, June 4–7, 2008. J Vet Intern Med 2008;22:723-724 (abstract)

Acknowledgments

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