

## **Update: Epilepsy and Canine Neurologic disease**

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Epilepsy and other neurological diseases strike at the essence of the animal; their mobility, their personality, their ability to enjoy life, if not life itself. Fortunately, molecular genetics and the canine genome project have provided the tools to advance our understanding of these devastating diseases.

In epilepsy, the contribution of genetics to the disease in several breeds has been clarified, and the genes responsible for several rare seizure disorders in dogs have been identified. It is hoped that finding the genes responsible for these rarer forms of epilepsy will ultimately solve the puzzle of the more common epilepsy syndromes. We found that one epilepsy syndrome in English Setters is caused by a mutation in the neuronal ceroid lipofuscinosis (CLN) gene CLN8. In humans, a mutation in CLN8 causes a syndrome called Northern Epilepsy. CLN, however, is a heterogeneous group of diseases caused by different mutations which produce other signs in various breeds. We identified a form of CLN in American Bulldogs that produced progressive loss of coordination and weakness. We found a mutation in the responsible gene (cathepsin D) and have screened almost 150 dogs for the mutation. We are currently investigating how this mutation leads to the disease. In Tibetan Terriers and Polish Lowland Sheepdogs, CLN is characterized by profound personality change as well as loss of coordination and vision. We have excluded the genes known to cause CLN in other breeds and species, and we have begun the task of mapping the responsible gene in these breeds. In addition to classic seizures, we have identified an unusual, familial syndrome in Chinooks, characterized by seizure-like episodes. Affected dogs have episodes of immobility and trembling, but do not lose consciousness or have the violent movements that characterize typical seizures. Several other breeds may also suffer similar episodes. We have also identified a syndrome in Standard Poodle pups (neonatal encephalopathy) in which affected pups develop poorly and die from intractable seizures by six weeks of age. The disease is inherited as an autosomal recessive. For both the Chinooks and the Standard Poodles, we have collected DNA from a pedigree sufficient to map the responsible genes.

Kerry Blue Terriers and Chinese Crested dogs suffer from multiple system degeneration, a hereditary movement disorder also called progressive

neuronal abiotrophy (PNA). We have mapped the gene responsible to a small segment of canine chromosome one. A gene which causes a very similar hereditary form of Parkinson's disease in humans (PARK2) resides in the homologous region of human chromosome six. Unfortunately, PARK2 is the third largest gene known, and thus far proving whether or not this gene harbors the causal mutation in these dogs has been challenging

Degenerative myelopathy (DM) causes progressive degeneration of the spinal cord and paralysis in older dogs. The disease has been recognized in German Shepherds for many years, but the cause of the degeneration has never been identified. More recently, DM has been recognized in other breeds including the Pembroke Welsh Corgi. We collected DNA, clinical data, spinal fluid, and post-mortem tissues from Corgis affected with DM. We have characterized the nature of the changes within the spinal cord of affected dogs. Several hypotheses regarding the cause of the degeneration were tested and have been excluded. The old-age onset of DM makes linkage studies difficult, but other techniques for identifying the responsible gene are being evaluated.