Report to Grant Sponsors

Both humans and dogs suffer from a large number of inherited disorders that lead to degenerative changes of the central nervous system. These diseases can cause such symptoms as visual impairment, loss of coordination, seizures, declines in cognitive function, paralysis, and ultimately death. Among these inherited neurodegenerative disorders are the neuronal ceroid lipofuscinoses (NCLs) and degenerative myelopathy (DM). NCLs and DM have been reported in a large number of dog breeds. To date, mutations in at least 8 different genes have been found to cause NCL in children. Dogs have versions of most of the genes present in humans. We previously have found the mutations in 3 genes that cause NCL in dogs: the CLN8 gene in English Setters, the CTSD gene in American Bulldogs, and the TPP1 gene in Dachshunds. We currently offer DNA tests for these mutations. Unfortunately, it appears that each NCL mutation is unique to a specific breed, and in fact more than one NCL mutation can occur in the same breed. Therefore, research must be done to identify the NCL mutation for each breed in which it occurs. A primary focus of our current research is to identify the mutations that cause NCL in as many breeds as possible. Over the past 6 months, most of our work on the canine NCLs has been focused on the forms of the disease that occur in Tibetan Terriers, Dachshunds and Australian Shepherds. In an Australian Shepherd with NCL we have found a mutation in the CLN6 gene that appears to be responsible for the disease. If you have an Australian Shepherd that is exhibiting symptoms of NCL (see our paper) or a dog closely related to the affected animal, please send us a blood sample and we will test for the CLN6 mutation at no charge. Tibetan Terriers suffer from a late-onset form of NCL in which the symptoms usually do not become apparent until the dog is more than 5 years old. As reported previously, we have tentatively identified the chromosome on which the Tibetan Terrier NCL gene is located. The location of this gene indicates that it is a gene that has not previously been associated with NCL in either dogs or humans. We are working to narrow down the precise location of the NCL gene in this breed so that we can determine its identity. We are still collecting samples from affected Tibetan Terriers and unaffected dogs of this breed that are over 10 years old. In the Dachshund breed, we have identified dogs with NCL that do not have mutations in the TPP1 gene. We are conducting analyses to identify this new Dachshund NCL mutation. Breed-specific descriptions of NCL symptoms in many breeds can be found at our website (http://www.caninegeneticdiseases.net/CL_site/mainCL.htm). If your dog exhibits a pattern of symptoms consistent with NCL, regardless of breed, we urge you to consult with your veterinarian and a neurology specialist if necessary. If other causes of the symptoms can be ruled out, we ask that you contact us as instructed on our website. For English Setters, American Bulldogs, Dachshunds, and Australian Shepherds with the appropriate symptoms, we will ask for a blood sample on which we can perform the DNA test for NCL. For all other breeds, we will request a blood sample and health and pedigree information (all information on specific dogs is kept confidential). We will use this sample and information to look for the NCL mutation in your breed. Our goal is to give every breed the tools necessary to screen for and eliminate NCL and other inherited neurodegenerative diseases.

We recently identified a mutation that is a major risk factor for DM in many dog breeds. We will announce a test for this mutation shortly. Meanwhile, if you have an affected dog that is going to be euthanized and are willing to donate tissues, please contact us.
Neuronal ceroid lipofuscinoses (NCLs) are inherited progressive diseases of the nervous system, with neurological symptoms including movement problems, visual impairment, seizures, loss of training, personality changes, and premature death. We have characterized a recessive late-onset form of NCL in Tibetan Terriers. Dogs can be carriers without showing any sign of disease and can pass on the disease to their offspring. With support from an earlier Acorn Grant, we had mapped the NCL mutation to a specific chromosomal position. In addition, we had identified a mutation at this mapping position that appeared to be causing the disease. With this Acorn grant we determined that the earlier identified mutation was not the cause of Tibetan terrier NCL. We then examined 7 additional nearby genes but did not find the mutation. We are continuing our search for the mutation responsible for Tibetan Terrier NCL under the auspices of AKC Canine Health Foundation grant 732 “Identification of Mutations Responsible for Hereditary Neurodegenerative Disorders in Dogs (Martin Katz, Principal Investigator).

Lens luxation is a debilitating inherited disease in which a defect of the lens suspensory apparatus leads to both lenses becoming loose within the eyes of adult dogs. This causes pain and damage to the eye, and commonly leads to glaucoma, threatening remaining vision. Treatment by surgical lens removal leads to major deficiencies in vision. The disease occurs in adult dogs of many terrier breeds, as well as Australian cattle dogs, Chinese crested dogs, Shar Pei dogs and border collies. We have used genomic mapping in two terrier breeds to define an interval in which the causative mutation must occur. There is insufficient variation in these breeds to allow fine mapping to identify the mutant gene. Under this grant we shall perform an analysis using Tibetan terriers that suffer from the same condition. Preliminary data suggests that the mutation is located at the same place in this breed. The current study will allow us to confirm the mutation responsible for PLL in Tibetan terriers is located in the same region of the genome as the equivalent mutation in the other two breeds and to greatly reduce the interval in which the mutation must occur. Candidate genes within the refined interval will be sequenced to define potential mutations.

Confirmed Updates:
- Dr Sargan has potentially narrowed the area of interest to search for a gene related to Lens Luxation to < 0.25 Mbp.
- For Tibetan terriers, the majority of the affected animals were heterozygous across much of the region although with a predominant haplotype which must be present at least once for lens luxation to occur. In all cases heterozygotes for the disease associated haplotype may not be affected. This is very preliminary data and can not be a detector of the disease at this time.

For those of you who are interested in the DNA bank at the University of Missouri, Liz Hansen sends this update on Lens Luxation:

“We are working on glaucoma and lens luxation in several breeds. If a breeder or owner has sent a sample for the NCL research they do not need to send another sample – if the dog was normal with respect to lens luxation or glaucoma (or epilepsy, and other concerns) at the time the sample was
sent in but now has that condition, we would very much like to hear from people to update us. Ask owners to send me an email with the dog’s registered name and number, call name, and the owner’s name, plus what status needs updating. We will update the records and include these dogs in the appropriate study. Anyone who has an affected dog or relative of an affected dog that has not yet been sampled is strongly encouraged to send those samples to us. Forms and instructions can be found by going to www.CanineGeneticDiseases.net, click on “Glaucoma & Lens Luxation” and then choose SAMPLE SUBMISSION.”

“Also, we have been working on degenerative myelopathy in several breeds, and have in fact mapped the mutation responsible in Pembroke Welsh Corgis and Boxers. We’ve found the same mutation at work in several other breeds known to have DM, and in surveying breeds in our collection, we have also found the mutation in breeds not known to have DM. Do you have any reports of this problem in Tibetan Terriers? We’d be very interested to know. If you need disease info, we have some up on a website – go to http://www.CanineGeneticDiseases.net and click on DEGENERATIVE MYELOPATHY. The discovery announcement is also on the CHF website.”

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As always, don’t hesitate to contact me with suggestions, questions or concerns.

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