

NCL was first identified in English Setters in the 1950's in Norway by veterinarian Nils Koppang. He started a research colony of these dogs that is still being maintained. At the University of Missouri-Columbia, we have been studying DNA samples from these dogs and have identified the mutation that causes the disease in this breed. A DNA test that can distinguish genetically normal dogs, asymptomatic carriers, and affected dogs is now available. Currently, it is not known if NCL still exists among privately owned English Setters. If it does, testing can help breeders avoid producing affected puppies. English Setters exhibiting NCL symptoms, or related to a dog exhibiting symptoms will be tested at no charge. See the SAMPLE SUBMISSION section of the NCL portion of www.CanineGeneticDiseases.net for instructions and forms.

NCL Description for English Setters

Age of onset of clinical signs: 12 to 18 months

Age of death or euthanasia: 19 to 27 months

Abnormalities often observed by the owner:

Mental changes: Affected dogs become “mentally dull” starting at 12 to 14 months of age. The decline in intelligence continues as the disease progresses.

Changes in gait and posture: English Setters with NCL develop a staggering gait with stiffness in all four legs. As the disease progresses, they develop a wide-based stance.

Visual abnormalities: Progressive loss of vision becomes apparent starting at 14 to 18 months of age, but the dogs do not appear to go totally blind, even at the end stage of the disease.

Seizures/convulsions: Seizures are a prominent feature of the disease in this breed. Seizures are usually not observed before 16 months of age. They become more severe as the disease progresses. A severe seizure usually precipitates death between 19 and 26 months of age.

Other changes: No changes in health other than those related to nervous system degeneration are observed in this disease.

Abnormalities observed upon clinical examinations:

Clinical neurologic changes: Electroencephalogram (EEG) recordings are abnormal in affected dogs, even before the onset of clinical manifestations. EEG abnormalities become more profound as the disease progresses. MRI shows substantial cerebral cortical atrophy late in the course of the disease.

Clinical ophthalmic changes: No clinical ophthalmic changes have been reported to date, but further investigation is required.

Visual abnormalities: The dogs develop severe visual impairment starting at around 14 months of age. By the end stage of the disease affected dogs are almost completely blind.

Retinal changes: Although affected dogs become visually impaired, the retina does not exhibit any degenerative changes that can be detected clinically.

Electroretinography (ERG): The electroretinogram c-wave was either decreased in amplitude, lacking or replaced by a negative wave.

Other clinical findings: None reported.

Histopathology

Brain: By the end of the disease process at ages over 20 months, the brain is grossly atrophic, weighing about 60-70% of that of normal English Setters. The atrophic brain is firm in consistency. The grisae are reduced and display a yellow discoloration. The ventricular system is dilated, especially the lateral and fourth ventricles, and the amount of cerebral spinal fluid is markedly increased. Practically all nerve cells of the cerebrum and cerebellum and most cells of the spinal cord show a progressive accumulation of autofluorescent lysosomal storage bodies. The accumulation of storage bodies does not appear to result in an increase in cell volume, but rather a replacement of normal intracellular constituents with the storage bodies. The ultrastructural appearance of the storage bodies is variable. Most storage bodies contain at least some material that has a membrane-like appearance. In some storage bodies, these structures are embedded in a granular osmiophilic matrix.

Eyes: Histologically, the retinas of affected dogs appear normal, with all of the retinal layers intact. Storage body accumulation has been reported in all neural cell layers of the retina.

Other organs and structures: Storage body accumulation occurs first in the nervous system, but as the disease progresses, characteristic storage material is found throughout the viscera. The degree of accumulation in different tissues is quite variable. Heart and skeletal muscle are least affected, whereas lymph nodes and the parotid and prostate glands are heavily involved. Outside of the nervous system, the massive accumulation of storage bodies does not appear to be associated with cell damage. No gross organ atrophy is observed. Lymph nodes are consistently enlarged.

Mode of inheritance: Autosomal recessive.

Gene containing mutation: CLN8. A DNA test is now available for English Setters with these symptoms.

References:

- Koppang N: English Setter model and juvenile ceroid-lipofuscinosis in man. *Am. J. Med. Genet.* 42: 599-604, 1992.
- Goebel HH: Retina in various animal models of neuronal ceroid-lipofuscinosis. *Am. J. Med. Genet.* 42:605-608, 1992.
- Katz ML, Khan S, Awano T, Shahid, A, Siakotos AN and Johnson GS: A mutation in the CLN8 gene in English Setter dogs with neuronal ceroid-lipofuscinosis. *Biochem. Biophys. Res. Commun.*, in press, 2004.