New cerebellar ataxia gene identified in dogs

June 18 2012

Researchers at the University of Helsinki and the Folkhälsan Research Center, Finland, have identified the genetic cause of early-onset progressive cerebellar degeneration the Finnish Hound dog breed. The study, led by Professor Hannes Lohi, revealed a new disease mechanism in cerebellar degeneration. A mutation was identified in the SEL1L gene, which has no previous link to inherited cerebellar ataxias.

This gene find is the first in canine early-onset cerebellar degeneration, and has enabled the development of a genetic test to help eradicate the disease from the breed. At the same time, SEL1L represents a novel candidate gene in human early-onset degenerative ataxias.

The research was published in the scientific journal *PLoS Genetics* on June 14, 2012.

Inherited ataxias affect both humans and animals. In humans, the hereditary ataxias are a heterogeneous disease group, characterized by cerebellar degeneration and dysfunction. The cerebellum is a part of the brain that is involved in coordination of movement. Degeneration of the cerebellar structures causes ataxia, which is a neurological sign of defective motor coordination that can affect gait, balance, speech and gaze. Approximately 20 known disease-causing genes have been identified in both autosomal recessive and dominant ataxias in humans but the genetic background of canine cerebellar ataxias has remained largely unknown.

The clinical signs of Finnish Hound cerebellar ataxia are present by the

age of two months. The affected puppies have difficulty in controlling their leg movements and keeping their balance. The disease progresses rapidly, and in the end eating becomes impossible because of uncontrolled head movements. There is no cure for the disease and affected puppies have to be euthanized.

The research conducted by Professor Lohi and co-workers revealed marked neuronal loss in the cerebellar cortex of affected Finnish Hound puppies. By comparing the genomes of affected and healthy dogs, the cause of the disease was pinpointed to a single nucleotide change in the SEL1L gene. The nucleotide alteration causes an amino acid change in the encoded SEL1L protein.

"The identified ataxia gene is the first early-onset degenerative cerebellar ataxia gene that has been identified in dogs", says professor Hannes Lohi. In addition to Finnish Hounds, cerebellar degeneration has been identified in several other dog breeds.

"The SEL1L gene has not been previously connected to cerebellar ataxias in any species and it represents a novel candidate gene for human early-onset ataxias", Lohi continues. "In fact, we have already screened a small cohort of human patients for possible disease-causing SEL1L mutations".

The gene identification in Finnish Hound dogs reveals a new disease mechanism, which will hopefully shed more light in to the pathogenesis of neuronal degeneration. The amino acid change in SEL1L hits an evolutionary conserved functional domain, and is very likely to affect the normal function of the protein. SEL1L functions in quality control of newly synthesized proteins, in a cell organelle referred to as the endoplasmic reticulum. A failure in the quality control system causes endoplasmic reticulum stress and eventually cell death.

"It is very interesting that although the SEL1L gene is expressed in several different tissues, we only saw pathological changes in the cerebellar cortex of affected dogs. It is known that certain neurons in the cerebellar cortex seem to be very sensitive to endoplasmic reticulum stress, which might offer some explanation to the cerebellum-restricted cell loss", tells M.Sc Kaisa Kyöstilä, the first author of the article. "We were also able to measure increased endoplasmic reticulum stress in the affected puppies' cerebellar cortex, which gives more support to SEL1L as the causative gene in Finnish Hound ataxia", Kyöstilä adds.

Finnish Hound ataxia is a single gene defect, inherited in an autosomal recessive manner. According to the research, 10% of Finnish Hounds carries the recessive ataxia mutation in their genome. A genetic test has been developed for breeding purposes. The test has enabled to identify disease carriers, and when mated with non-carriers, they too can be used in breeding programs. If all carrier dogs were excluded by breeders, the genetic diversity of the breed could be affected. The Finnish Hound ataxia test is offered by a DNA-test laboratory Genoscoper (genoscoper.com), and is the first test for a native Finnish breed developed by the research group.

Provided by University of Helsinki