Novel neurodegenerative disease and gene identified with the help of man's best friend

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Lagotto Romagnolo. Credit: Marko Saren

A breakthrough study performed in an international collaboration led by Professor Tosso Leeb from the University of Bern and Professor Hannes

Lohi from the University of Helsinki together with the veterinary neurologists and neuropathologists at the Faculty of Veterinary Medicine in the University of Helsinki has identified a gene mutation that causes a novel type of neurodegenerative disease in dogs. The results of the study shed light into the function of neurons, provide a new gene for human neurodegenration, and may aid in developing better treatments for neurodegenerative disorders. The study was published in the prestigious journal *PLoS Genetics* on 15.4.2015.

Finnish and Swiss investigators have made a genetic breakthrough in the Lagotto Romagnolo dog breed. The breed originates from Italy and is known for its skills in truffle hunting. These dogs have interested genetic researchers due to the existence of several rare neurological conditions in the breed. The current study revealed a novel type of neurodegenerative disease, characterized by cerebellar dysfunction and movement incoordination. Some affected dogs also suffered from abnormal eye movements and developed behavioral changes, such as restlessness and aggression. The onset of the clinical signs varies from 4 months to 4 years.

Gene discovery sheds light to a disease mechanism

Genetic analyses revealed a single nucleotide change in the ATG4D gene in affected dogs. The ATG4D gene functions as a part of an intracellular pathway called autophagy, which functions in normal cellular "cleaning" by degrading damaged cellular components and organelles. Autophagy plays also an important role in maintaining cellular functions under stressful conditions, such as nutrient deprivation. The affected Lagottos had signs of altered autophagy in the brain.

The ATG4D gene has not been previously linked to inherited diseases and represents an excellent candidate for human neurodegenerative disorders. "Our genetic finding enables more detailed future studies to

unravel the disease-causing mechanisms and to understand the role of autophagy in normal neuronal function. These results could also have a broader significance for understanding and treating neurodegenerative disorders", says Professor Hannes Lohi. Dogs could also help to explore novel therapy options for neurodegeneration.

Gene test helps breeding and veterinary diagnostics

This gene discovery enabled the development of a gene test to identify mutation carriers and to improve the Lagotto Romagnolo breeding program. "The genetic test not only helps in breeding decisions but can also be used for veterinary diagnostics. There are other similar neurodegenerative diseases in the breed and the genetic test can be used to get a differential diagnosis. This will also help ongoing studies in rest of the neurological disorders in the breed", tells the first author of the paper, PhD student Kaisa Kyöstilä. This study is a part of her doctoral thesis work.

"The signs and the rate of progression of the neurological abnormalities in this newly identified neurodegenerative disease vary considerably. The first clinical sign noticed by the dog owners can be episodes of abnormal eye movements (nystagmus) but in some cases the main clinical sign is a slowly progressive ataxia. The rate of progression of clinical signs varies from month to years. The diagnosis cannot be confirmed with clinical examinations and thus, the definitive diagnosis can only be made with the gene test" highlights Tarja Jokinen, a board-certified neurologist who participated in the studies at the University of Helsinki.

The study involved a team of geneticists, veterinary neurologists and pathologists from several different European countries and highlights the importance of collaboration between basic and clinical research in veterinary medicine.

More information: "A Missense Change in the ATG4D Gene Links Aberrant Autophagy to a Neurodegenerative Vacuolar Storage Disease." *PLOS Genet*. 2015. DOI: 10.1371/journal.pgen.1005169