Pompes disease in Finnish Lapphunds

Finnish researchers working in the University of Helsinki and Folkhälsan Research Center were able to identify a new disease causing mutation in dogs. A fatal Pompe disease seen in Lapphunds can now be diagnosed with a genetic test.

Pompe disease (also known as glycogen storage disease type II, GSD II) is a progressive disorder of glycogen metabolism that has been previously reported in Swedish Lapphunds. These initial studies have been performed in Netherlands in early 1980s. The population of Swedish Lapphunds in Finland is small and no affected dogs have ever been reported in Finland. However, now the research group received DNA samples from a Finnish Lapphund litter in which the same disease was diagnosed.

Symptoms of Pompe disease

Pompe disease affects humans as well. In humans there are over 300 mutations discovered from one gene, whereas in dogs the genetics of Pompe disease has remained a mystery so far. The severity of human disease varies a great deal depending on the causative mutation and the dogs' disease resembles the most severe infantile form of human Pompe disease. In Pompe disease there is a defect in breakdown of glycogen into glucose due to the lack of a certain glucosidase enzyme. Therefore, glycogen is accumulating in all cells of the body but the effects are most notable in energy consuming tissues (heart, skeletal muscles and smooth muscles). In dogs the symptoms of the disease involve coughing, recurrent vomiting of mucus, progressive muscle weakness and constant panting. Also delayed growth, heart abnormalities and dilated oesophagus leading to regurgitation are part of the disease progression. The disease is difficult to diagnose by veterinarians because none of the symptoms are disease specific. Blood chemistry shows abnormal liver enzyme values. Radiographs show dilatation of the esophagus and cardiac enlargement. The first symptoms become visible at the age of seven months and the symptoms progress so that usually the affected dogs either die naturally or are euthanized before the age of two years. There is no treatment for canine Pompe disease. The disease can also be diagnosed via post-mortem pathological examination.

Quick mutation discovery

The Canine Genetics Research Group led by Professor Hannes Lohi identified the disease causing mutation from a Finnish Lapphund litter. Out of seven puppies, four individuals became sick after the age of seven months. DNA samples were collected from two affected dogs that were still alive, their healthy siblings, parents and several other close relatives. Mutation was discovered soon after the samples arrived to the laboratory. Based on the previous literature, the researchers knew which gene to sequence in these individuals, as the same gene product is defect in human and dog patients. The identified mutation is inherited in autosomal recessive way meaning that the parents of the affected dogs were carriers (they had one copy of the mutation) and the affected dogs had two copies of the mutation.

The mutation was screened also from ~100 healthy Finnish Lapphunds and ~100 healthy Lapponian Herders. These samples were selected from the DNA bank that Professor Lohi has collected into his laboratory in the University of Helsinki during the past years. The samples have been collected mainly for genetic research of epilepsy and hereditary cataract, but they could now be used also in the Pompe disease study. The selection of samples was based on pedigrees. Researchers tried to pick up as many unrelated dogs as possible and the selection was done so that all individuals were unrelated at the grandparental level. Based on these sample cohorts, carrier frequency of 5% was detected among Finnish Lapphunds and 2% of the Lapponian Herders carried the mutation. However, no affected dogs have been reported in Lapponian Herders. This might be due to the difficulties in diagnosing the disease. The screening of current Swedish Lapphund population is still ongoing as there were not enough samples from this breed in the DNA bank.

Owners of the dogs that participated to the gene discovery and population screening have received the result of the genetic test for free. Other Finnish Lapphund, Swedish Lapphund and Lapponian Herder owners can order a commercial genetic test from Genoscoper (http://www.genoscoper.com). A sample that already exists in the DNA bank (University of Helsinki) can be used in the mutation testing. When making a gene

test order from an existing sample, it's necessary to add the information that sample already exists in the University of Helsinki DNA bank to the field "additional information" in the online order form.

Other genetic studies among Finnish Lapphunds

The genetic research of idiopathic epilepsy and hereditary cataract is still going on in the University of Helsinki. So far no genes predisposing to these inherited diseases have been identified from Lapphunds and the sample collection is active. The researchers collect samples especially from affected dogs and their healthy relatives. In addition, old healthy individuals are valuable controls in each study. In addition to the blood sample, researchers need health information of the dog and contact information of the owners. Therefore, when sending a blood sample from the dog please fill out also the sample form that can be found from the research group's web site www.koirangeenit.fi. For epileptic individuals, there is an additional epilepsy questionnaire. With this form the researchers collect important information from the type of epilepsy and seizures. For hereditary cataract study, the copy of an eye examination certificate is important. Please remember also to update the health and contact information if there are any changes after the sample submission. You can do this by email: eija.seppala@helsinki.fi.

Blood or buccal swab sample?

The genetic test of the Pompe disease can be done from DNA extracted from buccal swabs or from blood sample. If you order the test directly from Genoscoper, they will send you the buccal swab kits and instructions. You can also send a blood sample from your dog to the Canine Genetics Research Group at the University of Helsinki, and order the genetic test for Pompe disease from Genoscoper, stating that the sample exists in the University of Helsinki. One blood sample sent to the research group can be used both 1) for the commercial genetic test (Genoscoper) and also 2) to participate in the ongoing research projects at University of Helsinki. The University researchers are collecting blood samples because there is not enough good quality DNA for different genetic studies in the buccal swab samples.

The research group encourages all owners to report the result of the genetic test to the breed club, both in Finland and in your own country. The existence of this lethal disease was a surprise for all Finnish Lapphund and Lapponian Herder breeders and owners. The real mutation frequency and the actual risk lines within the breeds can be detected only by an open discussion of the test results. Finally, the research group would like to thank all the owners that have given a blood sample from their dogs to research purposes. Without the samples, this study would not have been possible.

The scientific article describing the results of the Pompe disease study has been submitted to a peer-reviewed scientific journal.

Related literature:

Walvoort HC. (1985) Glycogen storage disease type II in the lapland dog. The Veterinary Quarterly 7: 187-190.

Walvoort HC, Dormans JA, van den Ingh TS. (1985) Comparative pathology of the canine model of glycogen storage disease type II (pompe's disease). Journal of Inherited Metabolic Disease 8: 38-46.

Walvoort HC, Slee RG, Sluis KJ, Koster JF, Reuser AJ. (1984) Biochemical genetics of the lapland dog model of glycogen storage disease type II (acid alpha-glucosidase deficiency). American Journal of Medical Genetics 19: 589-598.

Walvoort HC, van Nes JJ, Stokhof AA, Wolvekamp WTC. (1984) Canine glycogen storage disease type II (GSD II): A clinical study of four affected lapland dogs. J Am Anita Hosp Assoc 20: 279-286.

Walvoort HC, Slee RG, Koster JF. (1982) Canine glycogen storage disease type II. A biochemical study of an acid alpha-glucosidase-deficient lapland dog. Biochimica Et Biophysica Acta 715: 63-69."

It is worth emphasizing some of the points coming out of the research.

1. **Pompe Disease (even if under-reported/misdiagnosed) is extremely rare**. The carrier rate in the study population is very low (5/100) and statistically not all of these dogs would be used for breeding. Furthermore, as it is in all 3 breeds, it is likely that the mutation has been in the population at a low level for a very long time.
2. If dogs are tested it will be vital to report results openly to aid the safe use of carriers in a breeding program. There is no reason why carriers could not be used.
3. It may be worth mentioning to your vet that the mutation has been found in the breed. At present, there is no written evidence of type II occuring in any other breed.

Finally, as scientific advances are made, more tests will gradually become available. It does not necessarily mean that our breed is becoming less healthy. It may, for example, not always be possible in the future to have breeding stock clear for all conditions if diversity is to be maintained. Increasingly, breeders will need to make multiple choices about the degree of risk they are willing to take with each pairing – and perhaps justifying their decisions to potential and existing owners.

Thank you to Ms Mary Starling for sharing this article from the Finnish Lapphund Club of Great Britain newsletter and to Dr. Eija Seppälä, PhD, of the Canine Genetics Group, University of Helsinki for the text material.