Institut für Genetik, Bremgartenstr. 109a, CH-3001 Bern

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Vetsuisse-Fakultät Universität Bern
Institut für Genetik

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Genetic Testing for Inherited Polyneuropathies in Leonbergers 2.0

Many Leonbergers suffer from forms of neurological disease collectively termed polyneuropathies. Affected dogs typically develop slowly worsening exercise intolerance, gait abnormalities such as an exaggerated hitched step, especially in the hind limbs, and often, wasting of the hind limb muscles. Additionally, these dogs often have noisy breathing, a change in their bark, or even difficulty breathing due to involvement of the larynx and laryngeal folds in the throat. Eventually the disease may progress to the point where the dog can no longer support its own weight.

A hereditary form of polyneuropathy, termed Leonberger polyneuropathy type 1 (LPN1), was genetically characterized in 2010 by the Universities of Minnesota, Bern, and California-San Diego, and a genetic test developed. The LPN1 test identifies dogs that have a severe disease with an age of onset less than 4 yr of age (mean = 2 yr). The LPN1 mutation is most likely inherited in an autosomal recessive manner. In other words, a dog must have two copies of the LPN1 mutation (i.e., a LPN1-DD genotype) to develop this form of disease, which explains approximately 20% of all diagnosed cases of polyneuropathy in Leonbergers.

We are excited to announce that a new genetic analysis of Leonbergers with polyneuropathy not attributable to the LPN1 mutation has identified a new gene mutation, termed LPN2, that is also highly associated with, and likely causative of polyneuropathy. LPN2 appears to explain approximately 25% of all diagnosed polyneuropathy cases; so, along with LPN1 we now have genetic tests that account for almost 50% of all diagnosed cases of polyneuropathy in this breed.

Unlike LPN1, LPN2 is a dominant condition, so a dog need have only a single copy of the LPN2 mutation (i.e., a LPN2-DN or a LPN2-DD genotype) to develop polyneuropathy. This has serious implications for breeders, as half of all offspring from a LPN2-DN dog will inherit a mutant D allele, and thus be genetically-susceptible to LPN2.

Universität Bern | Universität Zürich
vetsuisse-fakultät

Prof. Dr. Cord Drögemüller
Institut für Genetik
Bremgartenstr. 109a
CH-3001 Bern

Tel. +41 (0)31 631 25 29
Fax +41 (0)31 631 26 40
cord.droegemueller@vetsuisse.unibe.ch

Another complicating fact is that the age of onset of clinical signs in LPN2 affected dogs ranges from 1 - >10 years (mean = 6 yr), with ~ 80% of dogs with a LPN2 affected genotype show clinical signs of polyneuropathy by 8 yrs of age. This also has serious implications for breeders, as genetically-susceptible dogs may not develop clinical disease until late in life, if at all.

The Universities of Minnesota and Bern will start offering genetic testing for the newly-identified LPN2 mutation, to accompany our LPN1 testing, **starting July 15th, 2014** (for more details see below). At this time we recommend that all breeding dogs should be tested for both LPN1 and LPN2.

For LPN1 we continue to recommend avoiding matings that could produce LPN1-DD dogs, which at this time will most likely come by mating two LPN1-DN parents. Having only one LPN1-DN parent, with a LPN1-NN parent, will ensure that no LPN1-DD offspring will be born. In a global group of more than 4,000 Leonbergers which have been submitted to our laboratories since the discovery of the LPN1 mutation only about 1% were DD and 15% were DN, so breeding only LPN1-NN dogs should soon be possible without adversely affecting many desirable lines or the breed as a whole.

The situation with LPN2 is quite different, since on average 50% of the puppies from even a single LPN2-DN parent will be LPN2-DN, and 75% of the puppies from two LPN2-DN parents will be LPN2-DN or even LPN2-DD. Here we recommend a more aggressive approach by not selecting LPN2-DN dogs for breeding.

We can also state that relatively few dogs carry D alleles for both LPN1 and LPN2, as these two mutations are located on different chromosomes and are therefore transmitted independently, and that neither mutation is sex-linked. Furthermore, only ~ 5% of all Leonbergers carry the LPN2 mutation, so the carrier frequency is about 3 to 4 times lower than that of the LPN1 mutation.

Lastly, please remember that these tests diagnose only two of the possible genetic risk factors for polyneuropathy, and that affected offspring with a different genetic form of polyneuropathy can result even from a mating of dogs that both have been tested free for these mutations.

Summary of the LPN1 and LPN2 tests

	Mode of Inheritance	Susceptible Genotypes	Age of onset	Heritability Note
LPN1	Autosomal **recessive**	LPN1-DD	< 4 yr	Both parents must have at least one LPN1-D allele to produce affected puppies
LPN2	Autosomal **dominant**	LPN2-DN; and LPN2-DD	1 – >10 yr	Only one parent need have an LPN2-D allele to produce affected puppies

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Instructions for ordering the LPN1 and LPN2 tests in Europe

For genetic testing a 2-5 ml EDTA blood sample of the animal in question is required. The use of plastic tubes is recommended. Blood samples should be sent in a padded envelope by regular mail without cooling to our laboratory. They have to arrive within 3-4 days of sample taking. Order forms can be downloaded from: http://www.vetsuisse.unibe.ch/genetic/content/service/dog/index_eng.html

Please send the samples together with a signed order form to:

Institut für Genetik, „LPN test", Bremgartenstrasse 109A, CH-3001 Bern

The price per single test (either LPN1 or LPN2) on a single sample is 110 CHF or 75 EUR; however, the price for both tests (LPN1 + LPN2) on a single sample is **150 CHF** or **125 EUR**. The expected turnaround time is 2 – 8 weeks.

If a sample has already been submitted for the LPN1 test, and the result has been reported, the LPN2 test can be performed on this same sample for **50 CHF** or **40 EUR** after pre-payment onto the account of the Institute of Genetics (University of Bern): IBAN: **CH5309000000603151885,** BIC: **POFICHBE** (Postfinance, CH-3030 Bern). Please mention the lab ID (LB no.), after the receipt of your payment we will submit the LPN2 results by E-Mail or regular mail.

Dog owners who submit a blood sample from a dog affected with neurological disease, together with neurological exam or biopsy results, may receive the LPN1 & LPN2 test results for free.