1. What is Leonberger Polyneuropathy (LPN)?

Leonberger Polyneuropathy (LPN) is a collective term for several clinically similar neuromuscular diseases. The dog suffers from slowly worsening exercise intolerance and may develop gait abnormalities, such as an exaggerated "hitched" step, especially in the hind limbs. There is often wasting of the hind limb muscles. Additionally, these dogs may 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 cannot support its own weight. Biopsies of nerve from affected dogs show degradation of the nerve fibers and loss of myelin, the insulating material that normally helps speed messages along nerves. Muscle biopsies show atrophy resulting from nerve loss. Leonberger polyneuropathy is caused by at least two independent gene mutations. Genetic tests are available for LPN Type 1 (LPN1) and LPN Type 2 (LPN2).

Click here for a video of affected dogs.

2. Do the LPN1 and LPN2 tests identify all Leonberger dogs affected by (or carriers) for polyneuropathy?

No. Current data from nerve and muscle biopsy confirmed LPN cases indicates that the LPN1 mutation accounts for ~20% of LPN cases, and the LPN2 mutation accounts for an additional 20-25% of cases. Together these mutations account for ~40-45% of polyneuropathy observed in the Leonberger breed. There is strong evidence for at least one other as yet unidentified genetic polyneuropathy in the breed. This is similar to Charcot-Marie-Tooth (CMT) disorders in people, in which multiple mutations present with extremely similar neurological signs and histopathological changes. As of early 2010, mutations in >35 different genes have been identified as causes of CMT. Histopathological changes in CMT are usually classified as affecting the myelin or the axons of the nerve cells, or, in the case of intermediate forms of CMT, both the myelin and the axons. In the absence of a genetic test, it is important to obtain a nerve biopsy to confirm that a polyneuropathy truly exists, and that the clinical signs that a dog is presenting with are not being caused by other disease processes, such as spinal disc disease, heart failure, hypothyroidism, etc. Even in families with a history of LPN, other causes of clinical signs need to be ruled out. Finally, while histopathological examination of a nerve biopsy will indeed demonstrate characteristic changes of LPN (or CMT in humans), there are a very limited number of ways in which nervous tissue will respond to insult/injury. Therefore, several neurological diseases may look quite similar or even indistinguishable on a nerve biopsy. This is why it is vital to pair the nerve biopsy with as much additional information about the patient as possible (including clinical signs, any other tests that were performed, etc.)

3. What are the modes of inheritance of LPN1 & LPN2?

LPN1:

Current data strongly supports that LPN1 is inherited in an autosomal recessive manner. Dogs that are homozygous mutant (two copies of the LPN1 mutation) will typically develop polyneuropathy before they reach 3 years of age, and most dogs are quite severely affected. Some dogs heterozygous for this mutation (one copy of the mutation) have also been reported to develop clinical signs. However, whether these heterozygous dogs develop signs of polyneuropathy due to the LPN1 mutation or due to as yet unidentified mutations is not yet known with certainty. The identified LPN1 mutation appears to be responsible for ~20% of the cases of polyneuropathy in Leonbergers.

LPN1 genotypes:
- NN – clear
- DN – carrier/at risk
- DD - affected
**LPN2:**

LPN2 is inherited in an autosomal dominant manner. Dogs that are both heterozygous and homozygous mutant can develop polyneuropathy. The average age of onset in LPN2 affected dogs is 6 years of age (range: 1-10+ years, or never in their lifetime). In our research population, by 8 yrs of age, ~80% of dogs with the LPN2 mutation show clinical signs of disease. The identified LPN2 mutation appears to be responsible for ~20-25% of the cases of polyneuropathy in Leonbergers.

**LPN2 genotypes:**

- **NN** – clear
- **DN** – affected/heterozygous affected
- **DD** – affected/homozygous affected

The other ~55-60% cases are apparently caused by different genetic mutations.

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**4. Are LPN1 & LPN2 only found in Leonbergers?**

**LPN1:**

No. Although first described and researched in the Leonberger breed, we have since identified four St. Bernards that are homozygous mutant (two copies of the LPN1 mutation). All four of these dogs displayed the clinical signs of polyneuropathy. Therefore, we know that the St. Bernard breed has the identical mutation and it can cause clinical polyneuropathy in this population. The carrier rate of this mutation in a sampling of 383 St. Bernards was estimated at 1.8%.

The full extent of other breeds affected by the LPN1 mutation is unknown.

**LPN2:**

To date, the LPN2 mutation has only been identified in Leonberger dogs.

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**5. How prevalent are the LPN1 & LPN2 mutations in Leonbergers?**

Combining data from data from over 5,000 Leonbergers at both the University of Bern and the University of Minnesota, we have found these relative frequencies of the affected, heterozygous and clear states in Leonbergers:

**LPN1:**

- Affected (D/D) – 1.1%
- Carrier/At Risk (D/N) – 14.5%
- Clear (N/N) - 84.4%

**LPN2:**

- Affected/Homozygous Affected (D/D) – 0.3%
- Affected/Heterozygous Affected (D/N) – 6%
- Clear (N/N) – 93.7%
6. How many dogs that test clear (N/N) for both LPN1 and LPN2, have been diagnosed as polyneuropathy affected or presumed?

We have identified over 4,000 LPN1 N/N + LPN2 N/N Leonbergers to date. Within that group, we have 47 positive or probable biopsy confirmed cases (~1%). We have an additional 71 dogs (~2%) with either breathing and/or gait abnormalities that may or may not be attributable to polyneuropathy. The LPN cases amongst this group may be caused by another, as yet unknown, genetic mutation.

7. Should we only use clear (N/N) dogs for breeding? Are there any other breeding recommendations?

**LPN1:**

We don’t yet have enough data to answer this extremely important question. Until other potential disease-causing mutations are discovered, it is impossible for us to determine why some D/N dogs develop mild disease later in life. It could be due to the single copy of the LPN1 deletion, or it could be due to another form of disease (yet to be elucidated), or even a combination of the two.

As long as it is not absolutely clear that D/N dogs will all develop neurological disease, we recommend keeping them in the breeding pool for at least one generation. Litters of D/N x N/N matings should be tested and preferentially the N/N puppies should be kept for future breeding.

Immediately eliminating all LPN1 D/N dogs from breeding may have negative consequences for the genetic diversity of the breed. Important lines within the breed should be maintained, for example, if an important line is about to vanish, limited use of D/N animals may be used to preserve them. In other cases, it may be appropriate not to use any D/N dogs for breeding, if you “only” lose 15% of your population. This is not an overly dramatic loss of genetic diversity.

We were originally more cautious, because we did not know the exact frequency of carrier animals. As the predicted carrier rate has dropped from 25% to the more current estimate of <15%, this presents a good scenario for the sustainable eradication of LPN1.

We suggest a mid-term goal of reduction of the LPN1 allele from the breeding population. If eradication of LPN1 is desirable for a breed club, a complete ban of D/N animals starting in several years would represent a sensible measure in our opinion.

**LPN2:**

LPN2 presents a different recommendation. LPN2 is inherited in an autosomal dominant manner. Having even a single copy of the LPN2 mutation can cause disease. For LPN2, we recommend only breeding LPN2 N/N dogs.

**One final word of caution:** we do not yet know what other specific genes and mutations are causing polyneuropathy in Leonbergers. It is possible a LPN affected dog could still be produced, even from a mating of two LPN1 N/N + LPN2 N/N dogs. Therefore, we also recommend that both dogs in a breeding pair also be free of signs of LPN2, regardless of genotype.

See [Implications for Breeding](#) for diagrams of the different possible mating combinations.

8. Are the LPN1 and LPN2 tests 100% accurate? Have you had any evidence of false positives?
These tests are 100% specific test for a DNA segment deletion and these tests have proven 100% accurate for detecting these specific DNA segment deletions. There has been no evidence of a false positive to date.

9. What sample types are accepted for LPN1 & LPN2 testing?

At the University of Bern, only blood samples are accepted for genetic testing. A turnaround time of three months is guaranteed, but in general the clients get the results faster than that.

At the University of Minnesota, we accept blood (preferred), dew claws, cheek swabs, and semen.

Dew claws from the removed tissue of newly whelped pups can be tested, and, after a pup has been weaned for at least 24 hours, cheek swab samples can be accepted. Ideally, pups should be isolated from the dam and littermates for 1 hour before swabbing.

For blood sample testing, the dog should be old enough to have 1-3 ml of blood drawn by a veterinarian. Click here for instructions on submitting these samples.

*Please note that cheek swab samples may not yield sufficient quantities of high quality DNA for long term of storage.

10. If DNA is already available in the DNA bank, will the test fee be reduced?

Yes. For owners who have already received LPN1 tests result prior to August 2014, please contact lpninfo@umn.edu for instructions on how to receive your reduced fee LPN2 test result.

We will continue to provide free LPN1, and now LPN2 tests, to submitters of blood samples from affected dogs, if they also send us a copy of a qualified abnormal neurological exam together with normal thyroid blood test results, OR if they also send us the positive result of the histopathological examination of a muscle/nerve biopsy and/or nerve conduction study and EMG. For the University of Minnesota, if you are interested in submitting your dog’s sample for this free testing, you must contact us at lpninfo@umn.edu for special shipping instructions. Samples sent to the VLD will be charged normal testing fees.

11. Is research still ongoing to find the mutation(s) for the other version(s) of the disease?

The search for additional LPN mutations continues. We have strong indications for at least one additional inherited polynuropathy within the Leonberger breed. However, we do not have a solid lead on the location of the next LPN mutation yet. It may still take some time until genetic testing will become available. It is of utmost importance that we continue to receive samples from Leonbergers for our research at both the University of Bern and the University of Minnesota, especially from affected Leonbergers that have a biopsy confirmed diagnosis and are LPN1 N/N or D/N and LPN2 N/N.

At the University of Minnesota, samples submitted from affected Leonbergers that have undergone a neurological examination (which was abnormal) and testing to rule out thyroid disease are candidates for free LPN1 and LPN2 testing. If you have an affected dog that fits these requirements, please email Katie Minor at lpninfo@umn.edu in for special shipping instructions.

12. Are there any associated illnesses?

We have seen what appears to be an above average pattern of cruciate ligament injuries occurring early on in the lives of Leonbergers, who then go on to develop LPN. We have also seen an apparently above average
incidence of digestive issues occurring in LPN dogs. Is it possible that both of these conditions are connected with, or are perhaps exacerbated by, LPN? Does degeneration of the peripheral nerves in the hind legs make it more likely that a dog will damage its cruciate ligament? Does the laryngeal nerve have any association with the vagus nerve that could account for these reported episodes of reflux and dry vomiting?

A paper in *The Veterinary Journal* by Nicolas Granger entitled "Canine inherited motor and sensory neuropathies: An updated classification in 22 breeds and comparison to Charcot-Marie-Tooth disease" states the following: "Orthopaedic lesions can worsen the locomotor deficits and are sometimes considered as primary injuries, whereas they are in fact secondary to the neuropathy (e.g. due to lack of muscle support to the joints)." This seems to suggest exactly what has been suspected: the atrophy of the pelvic musculature or the degeneration of nervous stimulation to the muscles, may, in fact, predispose the dogs to cruciate rupture and perhaps other orthopedic injuries as well.

Gastrointestinal problems have been reported in CMT cases, so it is possible that similar problems could be occurring in Leonbergers with LPN. It is impossible for us to know at this time if the neuropathy extends to the vagal nerve. Historically, the laryngeal nerve(s) were presumed to be involved earlier in the disease process due to the extreme length of the nerve. Similarly, the nerves in the hindlimbs are quite long. It is within the realm of possibility that all nerves in the body are affected to some degree, including the vagus.