**LPN Research Update August 2011**

The following is an update on the present state of LPN research, prepared by Katie Minor at the University of Minnesota.

There are three aspects to this document. The initial update appears in standard text. This is interspersed with questions raised by the report, which appear in *italics.* Finally, there are answers from Katie Minor in reply to these follow-on questions, and these answers appear in **bold.**

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We have been working for about 1 year on a chromosomal area of interest for so-called "LPN2". We have sequenced five genes in this area without finding an obvious mutation to date. We have a few more genes that we could sequence.

It is also possible that our DNA sequencing approach, which mainly is capable of identifying simpler types of mutations, is not capable of identifying a more complicated type of mutation that may be causing LPN2.

Q. *Is there an alternative approach that you are considering?*

**A. We are considering a whole genome sequence of an affected dog.**

However, we are also seeing dogs that have neither LPN1, nor the DNA markers in the general region we are looking at for LPN2.

Q. *Are these dogs showing the characteristic signs of the illness*?

**A. Yes.**

Our lab, in collaboration with the lab in Switzerland, have sent an additional 48 polyneuropathy affected Leos for whole genome SNP association testing. Whole genome SNP association testing is the method that was used to find the chromosomal region containing LPN1 and to locate the chromosomal region we are searching for LPN2. Sometimes the regions are quite large relatively speaking with lots of genes, and sometimes the regions are relatively small. With LPN1 we got “lucky” and with LPN2 not so “lucky”. We are hoping that identification of an "LPN3" mutation might help us to find the LPN2 mutation as well by being able to attribute the population of non-LPN1 dogs into definite LPN2 and/or definite LPN3.

Q. *At this point do you believe there are more than three possible forms?*

**A. We won’t know until we get our newest data back.**

We do still very much want blood samples from affected dogs, and nerve biopsies to confirm PN in them (we recognize that for most dogs this will be post-mortem).

LPN1 STATS from Minnesota. (Far more dogs have been tested at Bern.)

3 DD St. Bernards, all with biopsy confirmed young-onset neuropathy.

*Q. What are your thoughts on these St Bernards in relation to the Leonberger breed? Are you adding this breed to the study now?*

**A. St. Bernards are one of the founding breeds of the Leonberger, and it may be that the LPN1 mutation was introduced by this breed. We have a few other St. Bernards with polyneuropathy, but far less than the number of Leos.**

Total Leos tested for LPN1 in Minnesota - 1174

35 DD (3%)
- 2 - under age 4, no signs
- 32 - with signs (21 with positive biopsy)
- 1 - with biopsy abnormalities, but no history

Average age of onset is 1.5 years

Seemingly ALL DD dogs will develop signs of neuropathy by 4 years

191 DN (16.3%)
- 88 - under age 6, no signs
- 19 - over 6, under 8; no signs
- 22 - 8 or older, no signs
- 60 – with some possible signs (22 with positive biopsy)

Average age of onset if signs do develop is 6.2 years

31.4 - 59.4% of DN dogs show some possible signs of neuropathy. We cannot be absolutely certain that these signs come from the one copy of the D gene for LPN1 or this is due to LPN2 or LPN3.

*Q. Do you see these D/N cases which are showing symptoms as being predominantly males or equally among males and females?*

**A. More males than females for all forms. This could be due to hormonal differences and their effect on nerves.**

948 NN (80.7%)
- 554 - under age 6, no signs
- 107 - over 6, under 8; no signs
- 137 - 8 or older, no signs
- 157 - with some possible signs (38 with positive biopsy)
  - We think 20 of these dogs may be attributable to LPN2

Average age of onset 6.4 years
16.6 – 39.2% of NN dogs showing some possible signs of neuropathy

Remember, this in by no mean a random sampling of Leonbergers, and is likely VERY biased toward dogs with signs of neuropathy.

We have sent our 48 best LPN1 NN cases for the LPN3 gene mapping effort.

*Q. By best do you mean either that they show the characteristic symptoms or simply that they have a family history (and perhaps confirmed by biopsy relatives?)*

**A. The most strong clinical signs (LP severe enough to require a tieback, severe breathing AND gait abnormalities, nerve conduction studies, or biopsy), and family history.**

At this time we still recommend that DN dogs (that are free of ANY signs of neuropathy) can be used if they are otherwise the most desirous choice for a breeding. Breeders should then select otherwise equal pups to go to breeder homes based on NN (clear) status for LPN1.

*Q. Have you considered, in the case of males, recommending that any such breeding wait until the dog has reached a certain age still free of symptoms?*

**A. That is not up to us, but not an unwise idea. Ideally, I would say 6 years of age, but I know this is not very practical in the real world.**

We will not certify a dog as being clear by parentage. OFA/CHIC will do this certification if the sire, dam and offspring are DNA parentage verified. This may be useful in the future, as other mutations are identified. One clear by parentage will certify a dog for every genetic disease for which both parents are clear. We have identified a case of incorrect parentage through LPN1 testing. We also caution that, as with anything in which humans are involved, the potential for error is possible, and we would recommend as a prudent practice to test dogs that are presumed clear by parentage if they are to be bred.

*Q. Have you had any further thoughts about the need to require proof of permanent ID for all test subjects, (in other words microchip or tattoo?*

**A. We will not require permanent ID to test dogs, but registering organizations/clubs could make that a requirement for posting.**

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Finally, it is worth pointing out that as this research is still very much an ongoing effort. Owners and breeders of Leonbergers can and should still play their part by continuing to provide DNA samples from untested Leos; Continue sending in the vital health updates on Leos who have already submitted DNA samples, (especially if their health or fitness has changed); And submitting nerve tissue samples from Leos who are suspected of having been affected with LPN. It would be of great value to this ongoing research effort if all clubs in the ILU made every effort to encourage their members to actively support the research in these ways.