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Hello Sharon,

Thank you for the opportunity to update everyone on our collaborative genetic studies of polyneuropathy (PN) and other neurological disorders in the Leonberger breed. You know most, if not all, of the history of LPN1 and LPN2 at both Minnesota and Bern. As Minnesota took the lead on publication of the LPN1 manuscript, we agreed that Bern should take the lead role in publication of the LPN2 mutation paper. We hope to have a draft of this manuscript by the end of the year at which time we can bring the Animal Health Trust into the picture. Here are some new or review points to keep in mind.

1. Breeding guidelines. We have no reason to change our breeding guidelines for dealing with LPN1, in that it still appears that two copies of the "D" (mutated) allele are required to show clinical signs; i.e. we still believe that LPN1 is a recessive condition. If a single LPN1 D allele does cause clinical disease we cannot distinguish it from the possibility that disease in such carriers is due to as yet unknown LPN forms.

The scenario for LPN2 is, unfortunately, that of a dominant condition that requires only a single copy of its D allele to cause clinical signs. This makes trying to decrease the frequency of the LPN2 D allele more urgent as a dog with a single copy of the D allele will pass it on to 50% of its offspring. Another issue with LPN2 is that approximately 20% of the dogs with the D allele may not show clinical signs over their lifetime. This is called reduced penetrance and is not an unusual situation in medical genetics.

2. Combined genetic testing figures from Bern and Minnesota now indicate that LPN1 accounts for approximately 20% of cases of PN, and LPN2 accounts for approximately 25% of PN cases. Thus, 45% of PN affected Leonberger dogs can be explained by the LPN1 and LPN2 mutations, and we assume that additional genetic and phenotypic heterogeneity in this condition exists in the Leonberger breed.

3. Bern has sequenced many non-LPN1 and non-LPN2 PN cases in an attempt to find mutations to account for a greater fraction of all PN diagnoses. In those sequenced dogs they looked specifically at just the sequences of 60 - 100 genes known to cause neuropathic conditions in people. The result is that there were several neuro genes which had mutations that could be considered "suggestive" for altering gene function in PN Leonbergers. Some of these potential mutations have been followed up now with genotyping in additional cases and controls both here and in Bern. Many candidate mutations have been deemed uninteresting because they are found in both cases and controls; in other words this whole genome sequencing approach can produce false leads.

However, one mutation that may someday be called LPN3 was not present in controls, and was present in a few additional PN cases. At Minnesota we currently have only two such cases with that mutation. The sequenced dog where the mutation was discovered did not develop PN signs until 6 yr old. And, there are many dogs with the "LPN3" mutation without signs of disease yet, but they are still quite young. So, we have not really agreed that this is worthy of being called LPN3 at this stage, and we don't know how significant an impact it will have on the overall picture of PN.

4. We are left with the conclusion that there are likely multiple genes and mutations in Leonbergers that can contribute to PN-like diseases. The PN disorders that we understand at this time are simple gene traits (LPN1, LPN2, perhaps “LPN3”, etc.). We must also consider that a fraction of the as yet unexplainable PN cases are not simple, but are more genetically complex, and result from combinations of mutations in multiple genes at the same time; this makes it difficult to unambiguously find the chromosomal locations with the current sample population.

5. We are considering whether more whole genome gene-mapping data must be gathered to improve our statistical power to identify these additional loci and enable more productive gene sequencing and mutation discovery work. Further, we all agree that that the whole genome sequencing of additional cases and scanning the genome for potential mutations, as for “LPN3”, is a way to proceed in attempting to explain more of the PN cases. The very large database of control dogs and dogs with health information available is an incredible resource and we remain hopeful that it can be made even better in the future.

6. Lastly, in collaboration with the University of Utrecht, we identified the chromosomal location of the gene for the LEMP nervous system disorder (leukomyeloencephalopathy). We have unfortunately and frustratingly been stuck at the stage of trying to identify a specific LEMP mutation from the whole genome sequencing data of a LEMP case. This region of DNA is very large and complex and the reference dog sequence with which we align all our Leonberger sequences has large gaps and inconsistencies that we are trying to fix one at a time. So, it is taking a long time and we cannot state for sure when we will find the LEMP mutation. We have a somewhat promising possibility, but it is not unambiguous. For this reason we are planning on sequencing another LEMP case, or maybe two.

Lastly, we would like to thank all Leonberger organizations and dog owners that have supported this research. We all feel honored to have been entrusted with this support.

Sincerely,

Jim Mickelson, PhD
Professor Veterinary Biochemistry and Genetics