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Leonberger Polyneuropathy (LPN): Research Update, September 2012

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Together with our collaborators from the University of Minnesota we continue to search for the genetic mutations underlying hereditary polyneuropathy in Leonberger dogs (LPN). Since we have identified the LPN1 mutation in the year 2010, we (and our partnering lab in the US) subsequently have been offering genetic testing as a service. We have genotyped more than 2600 Leonberger dogs in Berne for LPN1. We found about 15% LPN1 carriers (D/N) among the submitted samples (see appendix).

For LPN1 our recommendations remain unchanged: According to our data, every dog that is tested “affected” (D/D) in the LPN1 test will develop an early-onset and severe form of LPN. Clinical signs will typically become apparent before the dogs reach three years of age, occasionally symptoms may develop later until four years of age. Therefore, matings that could produce D/D puppies should be strictly avoided. There might be a certain risk for LPN1 carriers (D/N) to develop mild symptoms of LPN late in life. However, we don’t have enough data to quantify this risk. Thus, we don’t recommend the categorical exclusion of all D/N dogs from breeding. However, we advise a thorough evaluation of all other characteristics before D/N dogs are used in breeding. D/N dogs should be mated only to tested N/N dogs.

In 2011, we identified a second locus "LPN 2" for LPN and determine its chromosomal location. Our previous efforts to identify the causative mutation of this other form LPN by using established methods were not successful. Therefore, we have decided in this case to use a new and more comprehensive technology, which offers the possibility to decode the entire

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genome (the complete genetic material) of an individual within a few weeks. The necessary large equipment could be installed successfully, thanks to the support from the Swiss National Science Foundation in the spring of 2012 at the Institute of Genetics at the University of Bern. In the meantime, we have analyzed hereby two well-characterized PN affected Leonberger. Currently we are analyzing the resulting very large data sets to find PN associated DNA variants.

The situation in the case of LPN2 mutation is therefore not yet unchanged. Some mutations that lead to hereditary diseases are quite obvious and relatively easy to find. Other mutations are less obvious and consequently much harder to find. We found the LPN1 mutation only weeks after the initial mapping of the LPN1 locus. Unfortunately, LPN2 proves to be more difficult and we're looking for now using the more extensive data.

We think that there is at least one additional locus for LPN (which will become “LPN3”). To date, we have genotyped DNA samples from a total of 120 dogs LPN diseased on the current SNP chip at 170’000 markers. The results confirm the chromosomal location of the mutation LPN2, but unfortunately no clear indication of the presence of a single additional responsible gene locus. These results indicate that among PN affected dogs different subtypes exist, which we unfortunately cannot distinguish clinically, mix, and thus achieve any progress in mapping. Including, for example, could also probably a hereditary disorder of the central nervous system called leukoencephalomyelopathy (LEMP), which has been described in Leonberger dogs a few years ago by neuropathologists and clinicians of our small animal hospital for the first time. Dogs with LEMP show severe neurological signs of disease beginning in the first or second year of life. Currently we have 6 confirmed LEMP cases, which we want to use for the genome-wide SNP genotyping for possible mapping in the dog genome.

It is essential for our research that we continue to get blood samples and information on the health status of the dogs. Please notify us, once the health status of your dog changes, especially, if we have already a blood sample (e.g. dogs that were submitted for LPN1 testing). Once a dog that is not D/D at the LPN1 mutation starts to show clinical symptoms of LPN, please have this dog thoroughly examined. A histopathological examination of a muscle/nerve samples can be done on a biopsy or post mortem and is still considered to be very important for a definitive diagnosis.

We would like to thank all dog owners and breeders as well as our scientific collaborators for their continuing support.

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LPN1

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Land	N/N	D/N	D/D	Total
D	543	100	4	647
CH	295	53	3	351
NL	199	45	7	251
F	168	37	2	207
SF	171	14		185
CZ	153	21		174
S	154	14	1	169
I	117	18		135
B	88	13		101
NO	72	10		82
PL	45	1		46
DK	34	8		42
UK	29	7	1	37
LV	19	14		33
AT	19	11		30
HU	29	1		30
SK	19	3		22
RUS	19	3		22
IR	10	3		13
EST	8	2	1	11
E	8	1		9
BRA	3	3		6
USA	2	1	1	4
LT	3			3
UKR	1	1		2
Total	2208	384	20	2612

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