Update on polyneuropathy in Leonberger dogs

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Leonberger polyneuropathy (LPN): not two and through

- polyneuropathy (PN) characterized by **gait** and **laryngeal abnormalities** (high-stepping gait, stumbling, muscle atrophy, loss or change of bark, dyspnea, respiratory stridor, laryngeal paralysis, laryngeal tieback surgery)

breathing difficulties

hitched gait

muscle atrophy of the hind limbs

- **variable expression** of progressive clinical signs and ages of onset
- group of **clinically similar, but genetically distinct** diseases, similar to human Charcot-Marie-Tooth disease
- **LPN1**: autosomal recessive severe **early-onset** form, 10 base pair deletion within the ***ARHGEF10*** gene on CFA16
- **LPN2**: partially penetrant autosomal dominant **later-onset** form, frameshift mutation in the ***GJA9*** gene on CFA15

		LPN2 (GJA9) genotype		
	Total	***DD***	***DN***	***NN***
PN affected	**573**	**9**	**108**	**456**
LPN1 (ARHGEF10) NN	**389**	**5**	**75**	**309**
LPN1 (ARHGEF10) DN	**123**	**3**	**24**	**96**
LPN1 (ARHGEF10) DD	**61**	**1**	**9**	**51**
Non-affected (≥ 9 yrs)	**466**	**0**	**5**	**461**
LPN1 (ARHGEF10) NN	**409**	**0**	**3**	**406**
LPN1 (ARHGEF10) DN	**57**	**0**	**2**	**55**
LPN1 (ARHGEF10) DD	**0**	**0**	**0**	**0**
Population controls (young dogs & missing phenotype)	**6631**	**10**	**329**	**6292**
Total	**7670**	**19**	**442**	**7209**

53% of affected dogs do not carry either known mutation

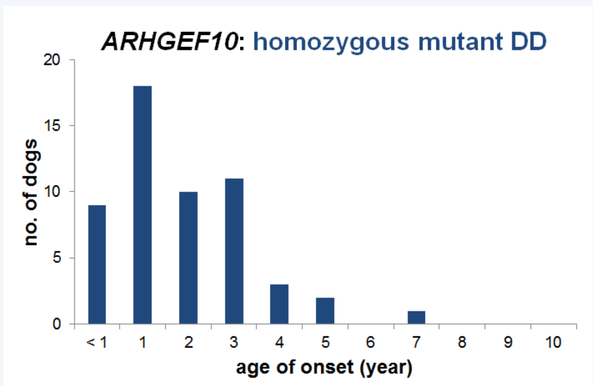
24% of unexplained cases are *ARHGEF10* heterozygous

→ **every third PN-affected dog can be explained by the two known mutations**

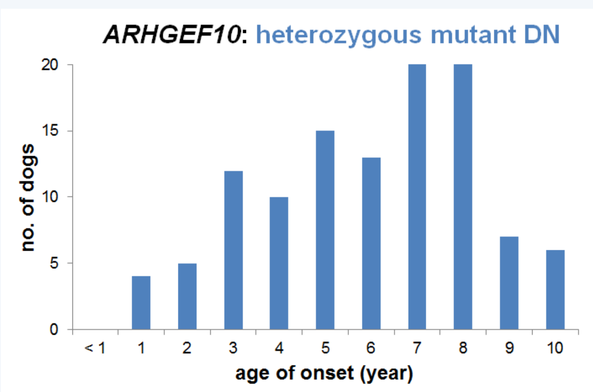
→ **additional genetic and phenotypic heterogeneity in this condition exists**

Age of onset for LPN1 (*ARHGEF10*):

- most homozygous dogs (DD) show PN signs before reaching 3 years of age

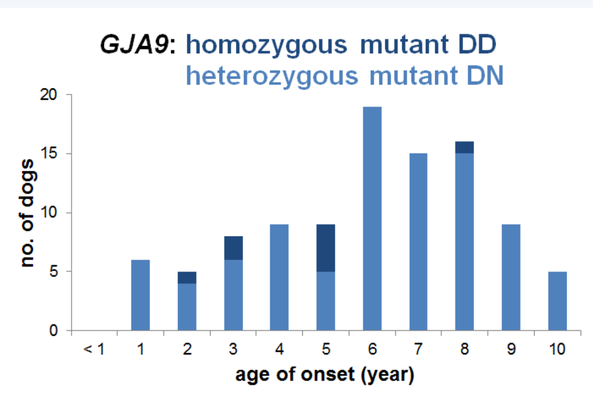


- heterozygous (DN) dogs are at risk for developing PN signs later in life

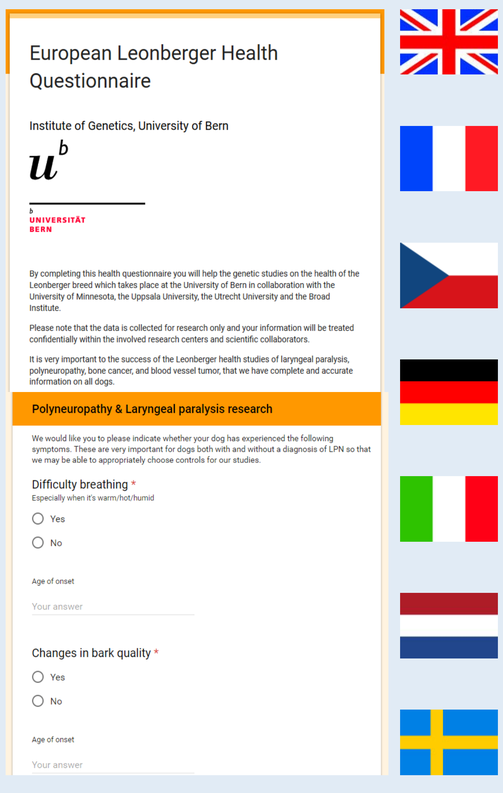


Age of onset for LPN2 (*GJA9*):

- 60% of affected dogs show signs by the age of 8 years
- the mean age of onset is 6 years



A dog is only as old as its last health update



European Leonberger Health Questionnaire

Institute of Genetics, University of Bern

UNIVERSITÄT BERN

By completing this health questionnaire you will help the genetic studies on the health of the Leonberger breed which takes place at the University of Bern in collaboration with the University of Minnesota, the Uppsala University, the Utrecht University and the Broad Institute.

Please note that the data is collected for research only and your information will be treated confidentially within the involved research centers and scientific collaborators.

It is very important to the success of the Leonberger health studies of laryngeal paralysis, polyneuropathy, bone cancer, and blood vessel tumor, that we have complete and accurate information on all dogs.

Polyneuropathy & Laryngeal paralysis research

We would like you to please indicate whether your dog has experienced the following symptoms. These are very important for dogs both with and without a diagnosis of LPN so that we may be able to appropriately choose controls for our studies.

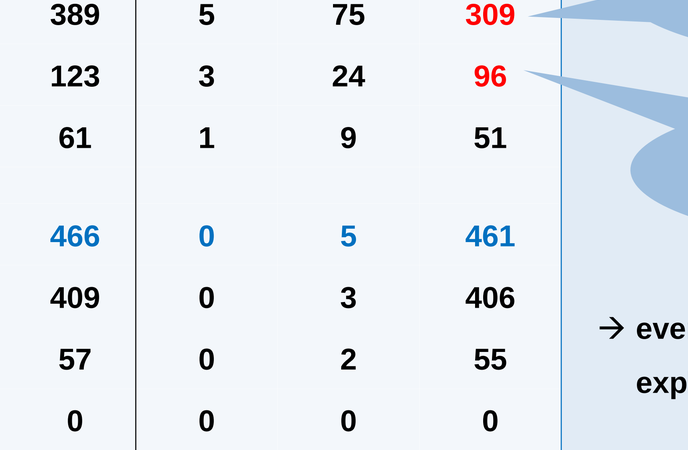
Difficulty breathing *
Especially when it's warm/hot/humid
Yes
No

Age of onset
Your answer

Changes in bark quality *
Yes
No

Age of onset
Your answer

Pedigree showing LPN affected dogs (in black)
(according to Shelton et al. (2003) Musle & Nerve 27: 471-7)



- after updating phenotypes additional related dogs showed signs of polyneuropathy (in red)
- genotyping of known LPN causing mutations

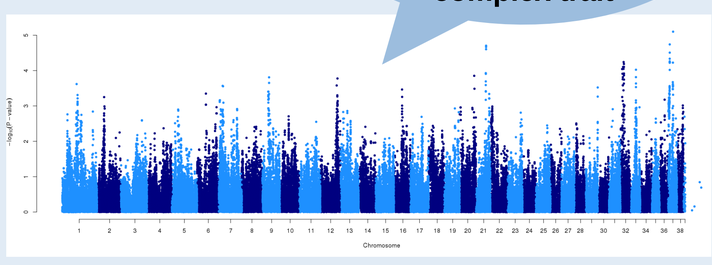
→ **exclusion** of initially suspected X-linked inheritance

→ no genetic explanation for some affected individuals confirmed **complex inheritance**

Towards GWAS mapping of further PN-associated loci in Leonberger dogs

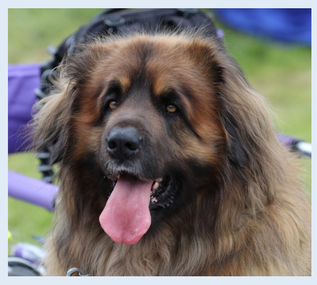
no significant association signal → polyneuropathy in Leonbergers is a complex trait

- Illumina CanineHD BeadChip 172/220k SNP arrays
- 224 cases & 142 controls
- only LPN1 (*ARHGEF10*) and LPN2 (*GJA9*) clear dogs (NN)
- R: GenABEL package



Outlook

- updating the health status of archived dogs
- SNP genotyping of additional cases and controls
- GWAS to detect further associated genome regions
- whole genome sequencing of affected and control dogs
- gene test development



Acknowledgments

We are grateful to the Leonberger Health Foundation (USA) and the Schweizerischer Leonberger Club (Switzerland) for supporting our research. Furthermore, we thank all dog owners, breeders and veterinarians for providing data and samples of both affected and healthy dogs.