

## **Interpretation of LPN1 genetic testing**

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**Free (genotype N/N):** Your dog is free of the LPN1 mutation for polyneuropathy. This means that your dog has two copies of the normal version of the analyzed gene, which is also referred to as homozygous normal or homozygous wildtype. This result does not exclude that your dog might have another form of polyneuropathy or that your dog might be carrier of a different polyneuropathy mutation.

**Carrier / at risk (genotype D/N):** Your dog has one normal and one mutant copy of the investigated gene. This is also called heterozygous. According to our studies, currently about 25% of all Leonbergers are carriers of the LPN1 mutation. It is possible that these LPN1 carriers develop a mild form of polyneuropathy starting after six years of age. However, LPN1 carriers do not get the severe early-onset polyneuropathy of LPN1 homozygote dogs. This result does not exclude the possibility that your dog additionally might have also another form of polyneuropathy or that your dog might be carrier of another different polyneuropathy mutation. LPN1 carriers will transmit the mutant form of the gene to approximately 50% of their offspring. The other 50% of their offspring will receive a normal copy of the gene from LPN1 carriers.

**Affected (genotype D/D):** Your dog has two copies of the mutant gene. This is also called homozygous mutant or LPN1 homozygous. Affected dogs will develop a severe form of polyneuropathy. The first clinical symptoms in these dogs normally manifest before they reach three years of age. Affected dogs will transmit one copy of the mutant gene to all their offspring.

### **Further information**

We analyze a specific sequence alteration in a defined gene that causes the LPN1 neuropathy. Our test is therefore a so-called direct genetic test. In so-called indirect genetic tests or marker tests, sequence alterations are analyzed that are not causative for a given trait. Therefore, the accuracy of a direct genetic test is superior to that of an indirect genetic test.

We use the letter D for the mutant form of the LPN1 gene and the letter N for the normal form of the LPN1 gene. Each dog receives one copy of this gene from its father and one copy from its mother. The combination of a dog's N- and D-copies is called genotype. The three possible genotypes are N/N, D/N, and D/D, respectively

(see above). All D/D dogs develop a severe form of polyneuropathy, which manifests before the age of three years. Dogs with the N/N genotype will not develop LPN1 polyneuropathy, they may however become affected by other forms of polyneuropathy. At the moment, it is not exactly clear, whether some or all D/N dogs may develop polyneuropathy. It is possible that some of these dogs will develop a mild form of polyneuropathy starting after six years of age.

**All possible genotype probabilities for breeding:**

Parents' genotypes	Probability for N/N-offspring	Probability for D/N-offspring	Probability for D/D-offspring
N/N x N/N	100%	0%	0%
N/N x D/N	50%	50%	0%
N/N x D/D	0%	100%	0%
D/N x D/N	25%	50%	25%
D/N x D/D	0%	50%	50%
D/D x D/D	0%	0%	100%

We strongly **discourage** the matings depicted in **red** !

In other words: From N/N x N/N or N/N x D/N you will never have a pup with the severe early-onset LPN1 polyneuropathy.

At this time we do not recommend to use exclusively N/N dogs for breeding. Carriers may be still used in breeding, if they are mated with homozygous free dogs. A strict exclusion of all carriers would narrow the restricted gene pool of Leonbergers too much. This might lead to an increase of other hereditary diseases. Valuable D/N breeding dogs should be used at the moment and will have 50% free offspring, if they are mated to N/N animals. The free offspring can then be used to select the best dogs with the desired traits for the next generation. The introduction of LPN1 genetic testing cannot completely eliminate polyneuropathy from the Leonberger population. LPN1 genetics testing recognizes only one of several genetic risk factors. Therefore, it is possible that even from the mating of two LPN1-free dogs offspring with a different form of polyneuropathy is born. However, LPN1 genetic testing can reliably avoid a severe early-onset form of polyneuropathy and this test can significantly reduce the overall frequency of polyneuropathy in Leonbergers.