Hereditary polyneuropathy in the Alaskan Malamute*

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Key words
Dog, electrodiagnosis, muscle- and nerve biopsy, segregation analysis

Summary
Objective: To prove the hypothesis that a polyneuropathy in Alaskan Malamutes has a genetic background. Material and methods: Pedigrees of 131 related Alaskan Malamutes were included in the current study. Neurological examination, electrodiagnosis as well as muscle and nerve biopsies could be performed in 10 dogs. Information about the disease status of the other 121 Alaskan Malamutes were supplied by referring veterinarians, breeders and owners. Segregation analysis using four different models (monogenic, polygenic, mixed monogenic-polygenic and the phenotypic model) was performed on 71 dogs to test the different mechanisms of genetic transmission. Results: In seven clinically affected dogs abnormal electromyographic findings and reduced nerve conduction velocity were detected. Suspected diagnosis of polyneuropathy was confirmed by nerve biopsy results, characterized by axonal degeneration and hypomyelination. Muscle specimens revealed signs of neurogenic myopathy. Three related clinically normal Alaskan Malamutes also displayed moderate neuromuscular changes in histopathology. In the segregation analysis the polygenic model proved as best suitable to explain the observed segregation pattern among all other models tested. Conclusion: The current study could demonstrate that polyneuropathy in Alaskan Malamutes is a hereditary disease with variable phenotypic expression ranging from severely affected to subclinical forms, which has to be considered in future gene analysis studies.

Schlüsselwörter
Hund, Elektrodiagnostik, Muskel- und Nervbiopsie, Segregationsanalyse

Zusammenfassung

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Introduction

Since the late 1970s various case reports about hereditary polyneuropathies in different canine breeds have been described such as the giant axonal neuropathy in German shepherds (11, 12), the progressive axonopathy in Boxers (16), the hypomyelinating polyneuropathy in the Golden retriever (3), the laryngeal paralysis-polyneuropathy complex in Bouviers de Flandre (24), young Dalmatians (6), young Rottweilers (17) and Siberian Huskies (21), the distal sensorimotor polyneuropathy in the Rottweiler (5), the hypertrophic neuropathy in the Tibetan terrier (8) and Mastiff (22), the sensory neuropathies in the English pointer (9, 10) and Dachshund (13), and the distal symmetric polyneuropathy in the Great Dane (2). A recent review was provided by Granger (15).

Also in Alaskan Malamutes a hereditary polyneuropathy has been suspected. The first affected dogs were examined in Norway between the years 1977 to 1979 by Moe et al. (18), Moe and Bjerkas (19) and Moe (20). A total of 12 dogs could be traced back to one common ancestor. Braund et al. (7) presented 11 cases of Alaskan Malamutes with polyneuropathy from different litters. Although the authors strongly suggested a genetic disease, several clinical, electrodiagnostical and histopathological differences to the dogs examined by Moe et al. (18) could be found. Using the term “idiopathic polyneuropathy in Alaskan Malamutes”, Braund et al. (7) distinguished this condition from the hereditary form previously described in Norway.

The objective of the present study was to elucidate whether a hereditary polyneuropathy exists in the Alaskan Malamute and to substantiate the clinical findings by electrodiagnostical, histopathological examinations and segregation analyses.

Material and methods

Dogs

A total of 131 Alaskan Malamutes were included in the present study (Fig. 1). Each dog received a number according to the information given by the breeders.

Initially, two Alaskan Malamutes were presented at the Department of Small Animal Medicine and Surgery, Veterinary School of Hannover, Germany, with a history of abnormal vocalization characterized by hoarse barking since three months, progressively decreasing muscle tone, weakness and exercise intolerance (dogs 52 & 53). Their littermates (dogs 51, 54, 55, 56 & 57), their parents (sire = dog 31, dam = dog 50) and four related dogs (dogs 30, 65, 66 & 76) were investigated. Another non-related and clinically healthy Alaskan Malamute of the same breeder was added as control dog. In collaboration with the breeders, a pedigree of 131 related dogs could finally be established. The ancestors of the Alaskan Malamutes examined in Hannover, Germany, were directly related with the Norwegian dogs (dogs 101–131) described by Moe et al. (18) and Moe and Bjerkas (19).

Clinical and neurological examination

General and neurological examination was performed on 10 Alaskan Malamutes (dogs 30, 31, 50, 51, 52, 53, 65, 66, 76 & the control dog). Concerning the remaining littermates (dogs 54, 55, 56 & 57), the information about the clinical status is based upon telephone calls with the referring veterinarians, the breeders or the owners.

Further examinations

Routine hematology and blood chemistry was performed on dogs 31, 50, 51, 52, 53 & 76. Additional examinations (T4, TSH, anti-acetylcholine-receptor antibodies) and edrophonium chloride testing (Tension®, Roche, 0.2 mg/kg BW) were performed on dog 52. Radiographs of thorax and abdomen were taken from dogs 31, 50, 51, 52 & 53.

For electrodiagnostic testing as well as muscle and nerve biopsies all dogs received general anaesthesia, which was induced by intravenous injection of diazepam (1.0 mg/kg BW) and levomethadone (0.6 mg/kg BW), and maintained by inhalation of isoflurane and oxygen. Electrodiagnostic testing was performed using a Nicolet Viking IV-D electrodiagnostic device (Würzburg-Höchberg, Germany). Electromyography (EMG) and motor nerve conduction velocity (NCV) on common peroneus and radialis nerve was tested on all 10 dogs previously undergoing neurological examination (dogs 30, 31, 50, 51, 52, 53, 65, 66, 76 & the control dog).

Muscle and nerve biopsies of seven Alaskan Malamutes (dogs 30, 31, 50, 51, 52, 53 & 76) were taken at the proximal lateral stifle level from the common peroneus nerve and the lateral head of the gastrocnemius muscle according to established surgical techniques (4). The biopsies were immediately stored in small plastic tubes and cooled using gel freeze packs without adding any fixative. They were transported to the Institute of Neuropathology of Heinrich Heine University, Düsseldorf, by overnight express.

Muscle specimens were orientated in transverse and longitudinal directions, embedded in tragant, frozen in isopentane at −135 °C, and stored in airtight plastic tubes at −80 °C. Cryostat sections of muscle and nerve specimens of 6–10 μm were stained with hematoxylin and eosin (H&E), and Gomori trichrome according to Engel; in addition, muscle specimens were treated with reduced nicotinamide adenine dinucleotide tetrazolium reductase (NADH-TR, pH 9.5), oil red O, myosine adenosine triphosphatase (ATPase, pH 10.0 and 4.3), and acidic phosphatase. In parallel, parts of the nerve specimens were fixed in a mixture of 2.5% formalin and 1% glutaraldehyde, buffered at pH 7.4, and processed for paraffin-histology or embedded in Epon, respectively. Semithin transverse sections were stained with toluidine-blue.

Pedigrees

The relationship between all 131 Alaskan Malamutes is shown in Figure 1. Information about the disease status of 121 Alaskan...
Malamutes was supplied by referring veterinarians, breeders and owners. This pedigree includes four nucleus families being paternal half sibs, which are connected to another affected pedigree member (dog 96) via their sire. A direct relationship between the four paternal half sib groups and the further affected members of the pedigree could not be found. The litter with the dogs 51–57 was inbred as well as the affected dogs 31, 50 and 76. Because information on the disease status of ancestors was often missing, the complex pedigree (Fig. 1A) was divided in two subpedigrees for segregation analysis: subpedigree-1 (Fig. 1B) including a total of 29 dogs and subpedigree-2 (Fig. 1C) with a total of 42 dogs. Dogs 93–95 and 97–100 of subpedigree-1 were reported to perform well.

Fig. 1 Pedigrees of 131 Alaskan Malamutes. A) complete pedigree, B) subpedigree-1, C) subpedigree-2.

▰ = male dog, ⬜ = female dog, ◊ = dog of unknown sex, ⚤ = not examined, grey filling of the symbols: clinically normal dog with positive histopathology, black filling of the symbols: clinically affected dog with positive electrodiagnostical and/or histopathological examination.
on the sled team and although not examined were considered to be clinically healthy.

In consequence, the segregation analysis included eight litters with a total of 71 Alaskan Malamutes.

Segregation analysis

The mode of inheritance was tested by employing complex segregation analysis models developed by Bonney (1) and Elston (14). The analysis was performed by using S.A.G.E., Version 3.0. The joint likelihood function for each pedigree was maximized conditionally on the phenotypes of the probands (dog 52 in subpedigree-2 and dog 131 in subpedigree-1). Ascertainment correction was applied as the pedigrees were non-randomly ascertained.

Clinically normal dogs with positive histopathology were coded with “1” (grey coloured in Fig. 1), clinically affected dogs with positive histological or/and electromyographical findings were coded with “2” (black coloured in Fig. 1). Four different groups of models were considered in the segregation analysis:

- Monogenic inheritance: This model assumes one gene locus with two alleles in Hardy-Weinberg equilibrium. The allele effects can be recessive, dominant or arbitrary. The transmission probabilities in this case are $\tau_{AA} = 1$, $\tau_{AB} = 0.5$ and $\tau_{BB} = 0$. The transmission parameter is the probability that a parent of genotype AA transmits allele A to offspring with genotype AA, AB or BB. The transmission probabilities are used to construct the genotypic probability distributions of offspring in dependence on the parental genotypes. Therefore, genotypes can be defined as types that transmit to offspring in Mendelian fashion.

- Polygenic inheritance: The effects of parents on offspring were regarded as logistic regressions. Three different submodels were specified. Submodel 1 (type of familiar correlation = 2) included the effect of the affected parents and spouses, submodel 2 (type of familiar correlation = 4) the effect of unaffected parents and spouses as well as the effect of affected parents and spouses. Submodel 3 (type of familiar correlation = 6) distinguished between affected sires, dams, and spouses as well as between unaffected sires, dams, and spouses.

- Mixed monogenic-polygenic inheritance (mixed major gene): This model described the inheritance by using monogenic and polygenic components as described above. The major gene effect was modelled as recessive, dominant or arbitrary effect in each of the three submodels for polygenic inheritance.

- Only one phenotypic distribution (µ-model): In this model only one phenotypic distribution with an arbitrary mean was used.

The different models were compared by using likelihood ratio tests. A saturated model (most general model) was fitted to the data and the likelihood of this model was used in the denominator of the likelihood ratio test. In the numerator of the likelihood ratio test the likelihood of the model being tested has to be nested in the model of the denominator. Then, the natural logarithm of the likelihood ratio multiplied by minus two is asymptotically chi-square distributed. Degrees of freedom for the likelihood ratio test statistic are given by the difference of the number of independently estimated parameters for the models compared.

Results

Results of neurological, electrodiagnostic and histological examinations are summarised in Table 1.

Clinical and neurological examination

Clinical examination of all dogs was normal. At neurological examination, all Alaskan Malamutes had normal consciousness, behaviour and posture. All dogs were pacing except dog 76.

In dog 52, gait analysis revealed tetraparesis with exercise intolerance. The postural reactions were generally decreased. Cranial nerve examination showed strong atrophy of the muscles innervated by the trigeminal nerve, and abnormal vocalization was characterized by a hoarse bark. Spinal reflexes were absent or markedly reduced. The muscle tone was reduced and a severe general muscle atrophy was noticed, especially on the hind limbs. Superficial and deep pain seemed to be normal or only slightly depressed. Affection of the phrenic nerve was suggested because of an abdominal type of respiration.

Dog 53 had similar, but less apparent signs. Dog 31 only displayed mild proprioceptive deficits in both front legs, dog 66 and 76 had slightly decreased postural reactions and spinal reflexes in the rear (Table 1). The remaining Malamutes (dogs 30, 50, 51, 65 & the control dog) showed no neurological abnormalities.

Two owners informed us, that dogs 55 & 56 also displayed deficits in form of abnormal vocalization, exercise intolerance and slight gait abnormalities, but refused any examinations.

According to the results of neurological examination, a generalised polyneuropathy was suspected.

Further examinations

Results of routine hematology and blood chemistry were normal. Additional testing performed on dog 52 excluded hypothyroidism (T4 = 1.5 μg/dl, TSH = 0.2 ng/ml) and ruled out myasthenia gravis by negative edrophonium chloride testing and absent anti-acetylcholine-receptor antibodies. Plain radiographs of thorax and abdomen (dogs 31, 50, 51, 52 & 53) were normal.

Electrodiagnostic findings

Electromyographic examination (EMG) revealed positive sharp waves in dogs 53 and 66 in interosseous, cranial tibial and quadriceps muscles. In addition, dog 53 had reduced insertion potentials in the muscles of the front legs. In dog 52, EMG was characterized by reduced insertion potentials, fibrillation potentials and positive sharp waves.
Motor nerve conduction velocity (NCV) from the peroneal or radialis nerve (Table 1) ranged from 60 to 93 m/sec in dogs 30, 31, 50, 51, 65, 66, 76 & the control dog and was reduced in dog 53 (29 m/sec). In dog 52, NCV could not be determined because of flat evoked potential curves. Dog 53 showed a slight decremental response on repetitive stimulation of the peroneal nerve.

Histopathological findings

Dogs with neurological deficits and positive electrodiagnostic findings had moderately to severely affected muscles. Pathological bimodal fibre size variation was the most prominent finding in dogs 30 (moderate), 31 (moderate), 52 (severe) and 53 (moderate) characterised by scattered angular atrophic as well as hypertrophic fibres (Fig. 2A). Both fibre types were involved, whereby most of the hypertrophic ones belonged to type 1, and most of the atrophic fibres to type 2 (Fig. 2B). Occasionally there was evidence of fibre type grouping. Some of the hypertrophic fibres had a slightly dystrophic shape. Myofibrils seemed to be normal, and no vacuoles or storage material could be found. Internal nuclei were rare. Fibre-splitting as well as clusters of myogenic nuclei as sign of regeneration occurred. Additionally, fibre degeneration and focal necrosis with phagocytosis (Fig. 2C) was observed. There was no evidence of inflammation in any of the specimens. Muscles of three clinically normal dogs (50, 51 & 76) were also affected: they had a slightly altered fibre calibre spectrum with individually disseminated – mostly angular – fibre atrophies.

Table 1

Neurological, electrodiagnostic and histopathological results in 12 related Alaskan Malamutes. EMG: electromyogram; NCV: nerve conduction velocity; f: female; m: male; ms: months; y: years.

<table>
<thead>
<tr>
<th>Pedigree-Nr.</th>
<th>Age</th>
<th>Sex</th>
<th>Neurologic signs</th>
<th>Electrodiagnosis</th>
<th>Histopathology</th>
</tr>
</thead>
<tbody>
<tr>
<td>30</td>
<td>11y</td>
<td>f</td>
<td>clinically normal</td>
<td>EMG: normal; NCV = 88 m/s</td>
<td>moderate degenerative polyneuropathy</td>
</tr>
<tr>
<td>31 (sire)</td>
<td>6y</td>
<td>m</td>
<td>postural reactions reduced in both front legs</td>
<td>EMG: normal; NCV = 62 m/s</td>
<td>moderate degenerative polyneuropathy</td>
</tr>
<tr>
<td>50 (dam)</td>
<td>3y</td>
<td>f</td>
<td>clinically normal</td>
<td>EMG: normal; NCV = 73 m/s</td>
<td>marginal degenerative polyneuropathy</td>
</tr>
<tr>
<td>51</td>
<td>1y</td>
<td>f</td>
<td>clinically normal</td>
<td>EMG: normal; NCV = 60 m/s</td>
<td>marginal degenerative polyneuropathy</td>
</tr>
<tr>
<td>52</td>
<td>1y</td>
<td>m</td>
<td>marked tetraparesis, exercise intolerance, pacing, depressed proprioception and absent spinal reflexes, general muscle atrophy including muscles innervated by the trigeminal nerve, abnormal vocalization</td>
<td>EMG: decreased insertion potentials, fibrillation potentials and positive sharp waves; NCV: no evaluation due to flat evoked potentials</td>
<td>severe degenerative polyneuropathy</td>
</tr>
<tr>
<td>53</td>
<td>1y</td>
<td>f</td>
<td>tetraparesis, proprioception and spinal reflexes reduced, abnormal vocalization</td>
<td>EMG: positive sharp waves, reduced insertion potentials, positive decremental response; NCV = 29 m/s</td>
<td>moderate degenerative polyneuropathy</td>
</tr>
<tr>
<td>55</td>
<td>1y</td>
<td>f</td>
<td>abnormal vocalization, exercise intolerance and slight gait abnormalities*</td>
<td>not performed</td>
<td>not performed</td>
</tr>
<tr>
<td>56</td>
<td>1y</td>
<td>f</td>
<td>abnormal vocalization, exercise intolerance and slight gait abnormalities*</td>
<td>not performed</td>
<td>not performed</td>
</tr>
<tr>
<td>65</td>
<td>2y</td>
<td>m</td>
<td>clinically normal</td>
<td>EMG: normal; NCV = 83 m/s</td>
<td>not performed</td>
</tr>
<tr>
<td>66</td>
<td>2y</td>
<td>f</td>
<td>proprioception and spinal reflexes reduced in the rear</td>
<td>EMG: positive sharp waves; NCV = 72 m/s</td>
<td>not performed</td>
</tr>
<tr>
<td>76</td>
<td>7m</td>
<td>m</td>
<td>proprioception and spinal reflexes reduced in the rear</td>
<td>EMG: normal; NCV = 65 m/s</td>
<td>marginal degenerative polyneuropathy</td>
</tr>
<tr>
<td>control</td>
<td>4y</td>
<td>m</td>
<td>clinically normal</td>
<td>EMG: normal; NCV = 81 m/s</td>
<td>not performed</td>
</tr>
</tbody>
</table>

* information provided by local veterinarian

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In endomysial nerve fascicles (Fig. 3A), as well as in peripheral nerve cross sections (Fig. 3B) of dogs 31, 52 & 53, alterations of the myelin-axon-relation were present. This was characterized either by axonal swelling, degeneration and/or demyelination, complete loss of myelinated fibres, Schwann cell proliferation, infiltrating macrophages and mild to moderate endoneural fibrosis. Signs of remyelination were reflected by very thin myelin sheaths, being inappropriate for the axonal diameter. In dogs 30 and 52, evidence of axonal necrosis was visible by myelin ovoids and balls (Fig. 3C). In the clinically normal dogs 50, 51 & 76, several degenerated and hypomyelinated axons in peripheral nerve fascicles were found.

**Pedigrees**

The prevalence of polyneuropathy among the analysed families was 29.6%. In total 21 affected animals could be either examined in our clinic or by the referring veterinarian. These puppies displayed weakness and reduced spinal reflexes. Among the affected puppies three were males, nine were females, and in nine affected animals the sex was unknown. The differences in prevalence of polyneuropathy among sexes were not significant (p = 0.153).

All families with affected puppies were related to each other. Inbreeding coefficients among litters varied from 0% to 20.0%. However, no significant differences in prevalences for polyneuropathy due to the inbreeding coefficient could be observed (p = 0.11).

**Segregation analysis**

The model with only one phenotypic distribution was compared with the monogenic, polygenic and mixed major gene models. The Mendelian models and mixed major gene models were not significantly different from the environmental model (μ-model, Table 2). The polygenic model with the logistic regression of offspring on affected parents and spouses explained the segregation significantly better than the environmental model. The further likelihood ratio tests compared the polygenic model with the Mendelian and mixed major gene models. The polygenic model fitted the data significantly better than the Mendelian models applied (Table 3). Also, the mixed major gene model could not improve the estimates of the polygenic model significantly, as was shown by the likelihood ratio test between these models. The likelihood ratio test of the polygenic model against the most general model was not significant indicating that the polygenic model fitted the data sufficiently well (Table 4).

Summarising the results of the segregation analysis the polygenic model proved as best suitable to explain the observed segregation pattern in the available pedigree. Thus, the hypothesis of a strong genetic background for polyneuropathy in this pedigree of Alaskan Malamutes was supported by the segregation analyses performed. Allowing the transmission probability for \( \tau_{AB} \) to vary in the mixed major gene model with arbitrary gene effects led to a
value of 15.66 for the –2log-likelihood with an estimate for $\tau_{AB} = 0.91$. This result also showed that mixed major gene models with transmission probabilities for Mendelian inheritance could not be fitted to this data set. A similar result was also found for monogenic models, when $\tau_{AB}$ was not fixed to a value of 0.5. The reason, why the monogenic and mixed monogenic-polygenic inheritance models could not sufficiently well explain the data was that the distributions of types in the pedigrees deviated significantly from genotypic distributions for Mendelian inheritance.

**Discussion**

The purpose of this prospective study was to evaluate, if the polyneuropathy found in the Alaskan Malamute breed has a genetic background.

In dogs 52 and 53, a sensorimotor polyneuropathy with severe clinical expression was suspected after neurological examination. Some of their relatives also had neurological deficits corresponding to a peripheral nerve lesion. However, these dogs were only moderately or subclinically affected, implying a polyneuropathy characterized by a wide range of clinical expressions. The observed neurological deficits (i.e. tetraparesis progressing to tetraplegia, exercise intolerance, inability to jump and walk up stairs, proprioceptive deficits, general hyporeflexia and severe muscle atrophy) were almost identical to those reported by Braund et al. (7). In contrast to Moe et al. (18) and Moe and Bjerkas (19) the Malamutes participating in our study displayed no signs of visceral nerve impairment (coughing, dyspnoea, regurgitation and megaoesophagus) except abnormal vocalization.

Electrodiagnostic testing had an excellent correlation to the clinical severeness of neurological deficits, however in contrast to histopathology electrodiagnostic work up was not sensitive enough to detect subclinical stages. This can be explained by the fact, that moderate demyelination and slight axonal degeneration does not necessarily influence NCV if a sufficient number of large and fast conducting nerve fibres are still present (23).

The histopathological changes resemble those described both by Moe et al. (18) and Braund et al. (7). According to the findings of Braund et al. (7), the peripheral neuropathy observed in our dogs is a primary axonopathy, characterised by axon swelling and degeneration, loss of myelinated nerve fibres as well as demyelination and remyelination in parallel. Neurogenic muscular atrophy of varying degree was present in all dogs. A new finding, however, is that the muscle fibre calibre spectrum was slightly to moderately irregular in three clinically normal Alaskan Malamutes. These dogs with slight but distinctive neurogenic myopathy and axonal changes are considered to be subclinically affected, an aspect we were able to describe for the first time in hereditary poly-
neuropathy in the Alaskan Malamute. In correlation with Braund et al. (7), histopathology revealed no signs of metabolic/toxic or immunopathological disease. Interestingly, at least two of our affected dogs were older than the previously reported (7) age of onset for polyneuropathy in Alaskan Malamutes (10–18 months): their age was 6.5 years (dog 31) and almost 12 years (dog 30). Due to their minor neuromuscular changes these dogs probably were able to functionally compensate their subclinical disease.

Table 2
Comparisons between the polygenic model and the other models under hypothesis using regressive logistic models for complex segregation analysis of polyneuropathy in Alaskan Malamutes.

<table>
<thead>
<tr>
<th>Tested hypothesis</th>
<th>df</th>
<th>–2 log likelihood</th>
<th>df-χ²</th>
<th>χ²</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>polygenic model</td>
<td>2</td>
<td>22.33</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>mixed model with</td>
<td>4</td>
<td>22.33</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>dominant major gene</td>
<td>6</td>
<td>22.33</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>mixed model with</td>
<td>2</td>
<td>20.35</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>recessive major gene</td>
<td>4</td>
<td>20.35</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>mixed model with</td>
<td>6</td>
<td>20.35</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>arbitrary major gene</td>
<td>2</td>
<td>21.72</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>mixed model with</td>
<td>4</td>
<td>21.72</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>arbitrary major gene</td>
<td>6</td>
<td>21.72</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

χ²: difference of –2log likelihood between the model under hypothesis and the polygenic model.
df-χ²: difference of the degrees of freedom between the model under hypothesis and the polygenic model.

Table 3
Comparisons between the polygenic model and the other models under hypothesis using regressive logistic models for complex segregation analysis of polyneuropathy in Alaskan Malamutes.

<table>
<thead>
<tr>
<th>Tested hypothesis</th>
<th>df</th>
<th>–2 log likelihood</th>
<th>df-χ²</th>
<th>χ²</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>polygenic model</td>
<td>2</td>
<td>22.33</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mendelian dominant</td>
<td>5</td>
<td>26.34</td>
<td></td>
<td>7.94</td>
<td>4 0.094</td>
</tr>
<tr>
<td>Mendelian recessive</td>
<td>5</td>
<td>27.50</td>
<td></td>
<td>6.78</td>
<td>4 0.148</td>
</tr>
<tr>
<td>Mendelian arbitrary</td>
<td>7</td>
<td>26.69</td>
<td></td>
<td>7.59</td>
<td>6 0.270</td>
</tr>
<tr>
<td>mixed model with</td>
<td>2</td>
<td>20.35</td>
<td></td>
<td>13.93</td>
<td>8 0.094</td>
</tr>
<tr>
<td>dominant major gene</td>
<td>4</td>
<td>20.35</td>
<td></td>
<td>13.93</td>
<td>10 0.176</td>
</tr>
<tr>
<td>mixed model with</td>
<td>6</td>
<td>20.35</td>
<td></td>
<td>13.93</td>
<td>10 0.176</td>
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<tr>
<td>recessive major gene</td>
<td>2</td>
<td>21.72</td>
<td></td>
<td>12.56</td>
<td>8 0.128</td>
</tr>
<tr>
<td>mixed model with</td>
<td>4</td>
<td>21.72</td>
<td></td>
<td>12.56</td>
<td>10 0.249</td>
</tr>
<tr>
<td>arbitrary major gene</td>
<td>6</td>
<td>21.72</td>
<td></td>
<td>12.56</td>
<td>10 0.249</td>
</tr>
<tr>
<td>mixed model with</td>
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<td>22.59</td>
<td></td>
<td>11.69</td>
<td>10 0.306</td>
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<tr>
<td>mixed model with</td>
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<td>12.78</td>
<td>12 0.385</td>
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<td>12 0.385</td>
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<td>6</td>
<td>21.50</td>
<td></td>
<td>12.78</td>
<td>12 0.385</td>
</tr>
</tbody>
</table>

χ²: difference of –2log likelihood between the model under hypothesis and the polygenic model.
df-χ²: difference of the degrees of freedom between the model under hypothesis and the polygenic model.
Table 4  Comparisons between the most general model and the polygenic model using regressive logistic models for complex segregation analysis of polyneuropathy in Alaskan Malamutes.

<table>
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<th>Tested hypothesis</th>
<th>Familiar correlation</th>
<th>df</th>
<th>-2 log likelihood</th>
<th>$\chi^2$</th>
<th>df-$\chi^2$</th>
<th>P</th>
</tr>
</thead>
<tbody>
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<td>17</td>
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<tr>
<td>polygenic model</td>
<td></td>
<td>2</td>
<td>6</td>
<td>22.33</td>
<td>13.56</td>
<td>11</td>
</tr>
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<td>8</td>
<td>22.33</td>
<td>13.56</td>
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<tr>
<td></td>
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<td>6</td>
<td>8</td>
<td>22.33</td>
<td>13.56</td>
<td>9</td>
</tr>
</tbody>
</table>

$\chi^2$: difference of $-2\log$ likelihood between the model under hypothesis and the most general model. df-$\chi^2$: difference of the degrees of freedom between the model under hypothesis and the most general model.

The present study could prove that the Alaskan Malamute polyneuropathy definitely has a hereditary nature. The hypothesis of a monogenic recessive inheritance for this polyneuropathy as suggested by Moe et al. (18) and Moe and Bjerkas (19) had to be rejected, since the distribution of affected dogs did not fit to the Mendelian ratios. This could be shown by two different tests in our genetic analysis. The most probable hypothesis that was accepted by the models used was a polygenic transmission from parents to offspring. This polygenic mode of inheritance may also explain the various phenotypic clinical expressions ranging from severe tetraplegia to subclinical stages. The number of genes responsible cannot be determined using complex segregation analyses as the number of possible models increases exponentially with the number of gene loci and alleles considered. A mixed model with a dominant major gene could not completely be ruled out, since some of the ancestors with unknown disease status could have been subclinically affected. Subclinical affected animals, which were not examined histopathologically, might be the cause that the mixed model could not be rejected and are a limitation to the study. Further investigations are warranted to clarify the genetic model and to identify possible mutations causing the Alaskan Malamute polyneuropathy.

Conflict of interest
The authors confirm that they do not have any conflict of interest.

Conclusion for practice
The current study could demonstrate that polyneuropathy in Alaskan Malamutes is a hereditary disease with variable phenotypic expression ranging from severely affected (weakness, tetraparesis, abnormal vocalization, abnormal performance as a sledge dog) to subclinical forms. Especially these subclinical forms have to be considered for breeding programs and future gene analysis studies trying to detect possible gene mutations.

References

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