Chapter 6

Heritability estimations of diseases, coat color, body weight and height in a birth cohort of Boxer dogs.

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**Summary**

Objective: Heritability estimations of diseases and animal characteristics in boxer dogs using different models as a basis for the development of genetic counseling programs.

Animals: A birth cohort of 2929 pure bred boxer dogs from 414 litters.

Procedure: Heritabilities were estimated for cheilo/palatoschizis, cryptorchism, epilepsy (two definitions), knee disorders (two definitions), heart disorders (three definitions), white coat color, birth weight, adult weight and shoulder height. All traits were analyzed with a mixed effects probit model; some traits were also analyzed with a model postulating a monogenic inheritance. The variation in disease incidences between clusters of related animals was studied.

Results: Heritability was virtually none for heart disorders, medium (0.17 to 0.36) for most other traits and high (>0.55) for coat color white, birth weight (but not adult weight) and height. Common environment for full sibs and risk factors notably affected cheilo/palatoschizis, heart murmur, epilepsy (in a broad definition, but not in a narrow definition) and adult weight. Heritabilities increased if stricter definitions for epilepsy and knee disorders were used. The monogenic model did not show higher heritabilities than the probit model, for six of the traits analyzed. White color showed the most significant different clusters (n=10). In most traits, there was a strong relation between the average breeding value per cluster and the prevalence in these clusters.

Conclusions: The results indicate that genetic improvement of most of these traits should be feasible except for heart disorders. However, as most of these traits were found to be influenced by environmental effects as well, genetic counseling methods using family information is preferred to strict exclusion of parents.
Introduction

Hereditary diseases are a major concern of the present purebred dog breeders. Therefore, screening programs have been developed and breeding rules were formulated for several breeds. Selection in dog breeding, to reduce disease frequency, is mainly based on exclusion of patients as parents or of parents with an undesired phenotype, for example in hip dysplasia. However, exclusion of affected parents from breeding is not necessarily effective. Firstly, if the disease is not heritable. Secondly, if the disease is multifactorial, for obvious reasons, exclusion of affected parents may be a relatively inefficient, crude or arbitrary measure. Exclusion of affected parents may thus lead to (unnecessary or too large) narrowing of the population, and thus to extra inbreeding.

Heritability is an important predictor of the success of selection, because heritability expresses the reliability of the phenotypic value as a guide to the breeding value. Heritability and breeding values can be estimated in different models. The probit model, very similar to a logistic model, was suggested by Wright to describe polygenic inheritance for a certain discrete trait. Probit (or similar) models allow to include environmental cofactors and random effects for common environment of full sibs and are therefore considered particularly suited for the investigation of multifactorial diseases and as a basis for genetic counseling for multifactorial diseases. To estimate heritability of a single-gene disorder other models were developed. Another way to investigate family aspects of diseases is the estimation of relative risks for diseases in clusters of related animals. An advantage of this method, cluster analysis, is, that no assumptions are needed about the pattern of inheritance, but at the other hand it is less suited for multifactorial diseases, because it can not adjust for environmental effects.

The aim of this report is to perform a first study of the heredity of several diseases and of some general characteristics based on survey data in Dutch boxer dogs. Investigated diseases were
selected, because a genetic background was known from literature or was assumed by boxer breeders and boxer owners.\textsuperscript{14-24} Heritabilities will be estimated using various models and will be compared with results from cluster analysis. The quality and usefulness of the survey data for heritability estimation will be discussed.

**Materials and methods**

**Population**

Data were collected from litters of the boxer population born in the Netherlands between January 1994 and March 1995. All dams had an official pedigree from the Dutch Kennel Club. All sires were registered in FCI (Fédération Cynologique Internationale) enlisted Kennel Club registration. In total 457 litters were born in that period and information was collected from 414 litters with 2629 pups.\textsuperscript{25} Breeders gave information about mortality, diseases and other problems until the pups went to their new owners. Also information about ancestry and the environmental situation in which the litter was raised was collected in this study period. The breeders received a note-book (Diary of the Boxer) for each pup. In this book information about the dog's health and preventive treatments could be collected. It also contained the objectives and methods of this study. The breeder forwarded these books to the new owners.

After weaning age, we separated the dogs in two cohorts. One dog from each litter was randomly chosen to be in the cohort that was monitored by telephone. All other pups were monitored by written questionnaires. Interviews and questionnaires were carried out every six months, starting at an age of six months, until February 1998. At this time, the oldest dogs were about four years old and the youngest dogs three years old. Data about survival, diseases and disorders of each half year were collected in these interviews.
Diseases and animal characteristics (traits)

The following diseases were analyzed in this study:

- **Cheilo**: Dogs with cheilolabial fissures, palatoschisis or cheilopolatschisis. The diagnosis was made by breeders, veterinarians or at postmortem examination.

- **Cryptorchism**: Canine cryptorchism was diagnosed by owners and/or veterinarians. We made no distinction between unilateral and bilateral cryptorchism.

- **Epilepsy**: Dogs with seizures diagnosed by owners or veterinarians were assumed to suffer from epilepsy and were classified as “Epilepsy” cases. When a dog displayed severe seizures more than once and the veterinarian diagnosed an idiopathic form of canine epilepsy or the dog showed a status epilepticus, the dog was additionally classified as “Severe epilepsy” case.

- **Knee**: A dog was lame in one or both hind leg(s) and a veterinarian diagnosed (by clinical investigation) knee problems. When further diagnostic work revealed cranial cruciate ligament rupture, fractured or ruptured meniscus, severe osteo-arthritis of the knee, or a combination of these disorders, the dog was additionally a case in the trait “Severe knee”.

- **Heart**: We distinguished three levels of heart disorders. When the dogs were four years old, we asked whether or not the veterinarian had auscultated the heart of the dog (at any age). If an abnormal heart sound was heard, the dog was a case in the trait “Heart murmur”. When further diagnostics were performed and there was ample evidence that there was a heart abnormality, the dog was additionally a case in the trait “Heart abnormalities”. This category contains accurately diagnosed abnormalities such as aortic stenosis and pulmonary stenosis as well as less certain diagnoses. For example: radiographic examination revealed an enlarged heart and a systolic murmur was heard, but no further diagnostics were performed. When an aortic stenosis was diagnosed with echocardiography or on postmortem examination, the dog was also a case in the trait “Aortic stenosis”.

The next animal characteristics were analyzed in this study:

- **White**: White coat colored boxers with or without spots of fawn or brindle on them.
- **Weight**: Birth weight was determined on the day of birth and registered by the breeder. The owners registered Adult weight for this study at an age between 2.5 and 3.5 years. Average weight and standard deviation were calculated in the pooled cohorts.
- **Height**: Shoulder height was measured at the withers at an age between 2.5 and 3.5 years, only of dogs of the cohort monitored telephonically. Average height and standard deviation were calculated.

Traits were either binomial (yes/no, presence/absence) or continuous (Weight and Height).

**Pedigree**

Ancestral data of the birth cohort was traced in records of the Dutch Kennel Club and merged with a second computerized data set.

**Statistical methods**

Prevalences of binomial traits were calculated by dividing the number of cases by the total number of cases and non cases (so missing cases were not included in the denominator). Mean and standard deviation of the continuous traits Weight and Height were calculated using SPSS (SPSS for windows, release 9.0).

**Heritability estimation: probit model**

To estimate heritability in a probit model, a software was used based on Janss and Foulley. The theoretical basis of the model used, and algorithms applied are described by Gianola and Foulley and Janss and Foulley. Variance estimation is based on an EM-REML algorithm.
In the probit model, all effects of parents are modeled as random effects and the variance component estimated for the parental effects is used to compute heritability of the trait. Three different estimates of heritability were performed. Firstly, heritability was estimated in a model where only the disease status and the pedigree were included. In a second model the litter was also included (as random effect), to correct for maternal effects and common environment for litter mates, during pregnancy and weaning period. The third model included the disease status, the pedigree, the litter (as a random effect) and known or suspected risk factors from literature (as fixed effects).

Heritability estimation: Single gene model

A monogenic model (bi-allelic, autosomal) was fitted using a Monte Carlo Markov Chain (MCMC) algorithm. A relaxation technique, and blocked sampling of genotypes was used to improve convergence.\textsuperscript{29-30} For some analyses two levels of relaxation appeared to be required for proper convergence, implemented as with the simulated tempering sampler of Geyer and Thompson.\textsuperscript{31} Using the notation of Falconer, the 3 genotypes for this model are aa, Aa and AA, with frequencies in the founder population of $q^2$, $2pq$ and $p^2$, assuming Hardy-Weinberg proportions.\textsuperscript{8} The penetrance functions, the probabilities of sickness given a certain genotype, we have denote as $\lambda_{aa}$, $\lambda_{Aa}$ and $\lambda_{AA}$. The restrictions $\lambda_{aa} > \lambda_{Aa}$ and $\lambda_{aa} > \lambda_{AA}$ were applied, so that aa will be the genotype with the highest probability of sickness and $q$ is the frequency of the putative disease allele. The MCMC scheme of Sheehan and Thomas was extended to estimate the model parameters ($q$, $\lambda_{aa}$, $\lambda_{Aa}$, $\lambda_{AA}$) in a Bayesian way, by adding to the MCMC the sampling of these parameters from beta distributions with flat priors.\textsuperscript{29-30} For estimation of parameters, repeated Markov chains of 200000 cycles were generated, until a minimum of 100 independent samples for all parameters was obtained, judged by comparison of within- and
between chain variances. Heritabilities for the monogenic model were computed on an underlying probit scale, using the inverse probit function to transform penetrance probabilities to genotype means on the probit scale and subsequently computing the variance of genotype means. A broad sense heritability ("total", including dominance variance) and a narrow sense heritability (additive variance only) were computed.

Genetic cluster analysis
To group the boxers into clusters of related dogs (relatedness > 0.125) a hierarchal cluster analysis with average-linkage-between-clusters was applied on a matrix of relatedness between all dogs of the birth cohort. Of all binomial traits, prevalences were calculated per cluster and the relative risk (R R) of a cluster, relative to the total cohort, was calculated using: 

\[ R_{\text{cluster}} = \frac{P_{\text{cluster}}}{P_{\text{birthcohort}}} \]

In this formula, \( P_{\text{cluster}} \) is the prevalence of a trait in the cluster, the \( P_{\text{birthcohort}} \) is the prevalence of the trait in the total birth cohort. The 95% confidence intervals (CI) of these RR were calculated using:

\[ CI_{\text{min}} = e^{\text{ln}(R R) - 1.96 \sqrt{\text{var}[\text{ln}(R R)]}} \quad \text{and} \quad CI_{\text{max}} = e^{\text{ln}(R R) + 1.96 \sqrt{\text{var}[\text{ln}(R R)]}} \]

Clusters with confidence intervals of the RR with a minimum value higher than 1 or a maximum value lower than 1, were considered significantly different from the total population.

We calculated the correlation coefficient of the prevalence of clusters of each trait and the average breeding value of clusters. Scatter plots of the prevalence and average breeding value of high, average and low correlations were created. Breeding values of the dogs in the birth cohort were obtained as the average breeding value of each dog's parents, where the latter were available from the probit model.
Results

The mean birth weight of 1705 pups was 486 grams (sd 84). Average adult weight in 1163 boxers was 31.66 kilogram (sd 5.05). The shoulder height was only measured by owners participating in “the telephonic cohort” and the average height of 210 boxers was 60.67 centimeter (sd 4.81).

Cryptorchism had a prevalence of 10.7% and this was the highest prevalence of all traits included in this study. Other traits with prevalences higher than 5 were Heart murmur (9.7%) and White (8.7%). A mortality rate of 100% was found in Cheilo. Epilepsy (40.8%), Severe epilepsy (55.8%), Aortic stenosis (41.7%) and White (44.9%) showed also high percentages of mortality (Table 1).

Estimates of the heritability are figured in Table 2 and Table 3. Birth weight ($h^2$ corrected = 0.62), White ($h^2 = 0.61$) and Height ($h^2 = 0.53$) showed high heritabilities in the probit model. In the single gene model White had a high heritability ($h^2$ additive = 0.34).

Heritability estimates decreased for the disorders Knee and Epilepsy when not only cases with an accurate diagnosis were included, but also less certain cases. In most traits, heritability decreased when corrected for litter and risk factors. Only Birth weight showed a considerable increase. All heart disorders showed low heritability estimates.

Confidence intervals of relative risks of traits in most genetic clusters included one, so prevalences of these traits in these clusters were not significantly lower or higher than in the total population. White had the most significant different clusters, namely 10 clusters. The other traits had 0 to 3 clusters with significant lower or higher prevalences (Figure 1).

The strength of the relations (Table 4) between the average breeding value of a trait per cluster and the prevalence of this trait per cluster was high in most traits (correlation coefficient was between 0.7 and 0.89). Cryptorchism, Epilepsy (all cases) and knee (all cases)
showed lower correlation coefficients (Table 4). Some examples of scatter plots of prevalences and average breeding values of clusters illustrate the differences in correlation (Figure 2).

**Discussion**

In this study the heritability of diseases, coat color white, weight and height was estimated in a birth cohort of 2629 boxers. Prevalences of diseases and white, up to four years of age, were between 1.7% (Severe epilepsy) and 10.7% (Cryptorchism). Up to four years of age, the prevalence of some traits, for example Severe epilepsy and Aortic stenosis, was not high (respectively 1.7% and 1.3%), but mortality was high (respectively 55.8% and 41.7%). The high mortality rates of 100% for Cheilo and 44.9 for White were mainly caused by the breeders’ decisions to euthanase pups with cheiloschizis, palatoschizis or cheilopalatoschizis or a white coat color.

Although we didn’t have complete pedigrees of all boxers of the birth cohort, in the fifth generation 85% of the ancestors was known. Therefore, we considered the quality of these data to be good enough to estimate an accurate relatedness between the boxers in the birth cohort.

In general, the results showed medium to high heritabilities with most diseases in the medium range and White, Birth Weight and Height in the high range. Only Heart traits showed very low to virtually absent heritabilities. Different models altered little to the general conclusions. Inclusion of permanent environmental effects for full sibs and of additional risk factors notably affected Cheilo, Epilepsy and Adult Weight. Monogenic models showed generally lower heritabilities, such that for none of the traits investigated a monogenic model appears plausible.

The clustering procedure also indicated White to have a clear association with familial lines; White was found the most heritable trait in the probit model. Average cluster breeding values
and cluster incidences showed a good correspondence, except for Cryptorchism and Epilepsy. This suggests that the additive model of inheritance could be incorrect. Because Epilepsy and Knee-problems are very likely a mixture of diagnoses, low correlation coefficients in these traits could be possible. Some studies on cryptorchism disagree about the mode of inheritance.\textsuperscript{16,34} Because of this disagreement in both literature and in this study, more research into the genetic aspects is suggested, before starting genetic counseling of cryptorchism. For example, by separating maternal and paternal contributions to the inheritance as done by Janss and Brascamp.\textsuperscript{35} The accuracy of heritability estimations could be evaluated in the monogenic models and yielded standard errors of heritabilities around 0.10. The single gene model estimated heritability in the broad sense (\( h^2 \) total) and in the narrow sense (\( h^2 \) additive). Which of the estimations is to be used, depends on the goal for which the estimated heritability is used. The additive genetic component is most useful for genetic counseling, because it determines the degree of resemblance between parents and offspring.\textsuperscript{8} Cheiloschizis, palatoschizis or cheilopalatoschizis in other studies are described as having a genetic background, although the mode of inheritance differs in the studies.\textsuperscript{15, 17, 36-39} The relatively high heritability of epilepsy, although not as high as Famula found in Belgian Tervueren, is interesting, because epilepsy in boxers is often severe and it was the disorder with the highest mortality rate in Boxers between weaning age and four years (Nielen 1999, unpublished data). In a few recent studies, in different breeds the genetic background of a dog is a major risk factor of epilepsy.\textsuperscript{21, 23, 40-43} The high heritability level suggests that genetic counseling, based on the breeding values, found in the same models that are used in this study to estimate heritability,\textsuperscript{27-28} can help to select parents in such a way that the prevalence of epilepsy will decrease.\textsuperscript{44}
Estimations of heritability of knee-problems were performed in two ways: proved knee-problems and proved or suspected knee-problems. For both traits we corrected the known risk factors, because next to breed, also body weight, age, and sex were known as risk factors. The heritability of the proved cases was much higher than the heritability of the proved and suspected cases (respectively 0.28 and 0.15 in the probit model). Therefore it is very likely that improved diagnostics on knee-problems, will be useful to increase the results of genetic counseling.

All three cardiac traits had low heritability estimations in all models (varying from 0.00 to 0.09). In more studies the occurrence of heart abnormalities differed between breeds and this is often considered an indication for diseases to have a major genetic background. Our finding does not subscribe these findings. Therefore, we suggest that, in the next four years of this boxer follow up study cardiac problems will have extra attention.

According to literature, the genotype of white colored boxers is $s^w$ and this s-locus is the only locus responsible for extensive white in Boxers. Assuming a monogenic inheritance with a complete dominance, a Hardy-Weinberg equilibrium and a prevalence of 0.087 (the prevalence for White in this study), an additive heritability of 0.46 is expected. In that case the remaining variance should be the dominance variation. We found an (additive) heritability of 0.61 in the probit model, so based on this result, a monogenic, complete dominance trait is possible. However, the single-gene model did not support this assumption. In this model a total heritability (additive and dominance) of 1.0 is expected, with the same assumptions as mentioned above. However, we estimated a heritability of 0.53 and also the 90% confidence intervals did not include 1.0. Two explanations for this finding are possible. First, the assumption of monogenic inheritance, with complete dominance may not be correct. Second, the phenotyping is maybe incomplete, because not all cases were reported. Fifty percent of the
white boxer pups were euthanased immediately after birth. Breeders easily could withhold this information. In another study of this boxer cohort this lack of information was not confirmed, however.25

Knowledge of the heritability is useful in genetic counseling for calculating recurrent risks in families because it allows all the information about the family to be combined correctly. Individual selection of disorders with a binomial distribution is mainly based on the prevalence of the disorder, whereas in continuous characters the proportion of selected ancestors is more important.8 In rare diseases and disorders with a low heritability, family selection will be more efficient than individual selection.8,53 Defining families in purebred dog population is complicated and therefore we used a method which assigns related dogs to a cluster.13 Differences in prevalence of traits between clusters would give information about the distribution of a trait in the population, while breeding values of animals within clusters could be useful in selecting parents for mating.

In conclusion, several traits show medium-high heritabilities (20% and more), which indicates good prospects for change by selection. This applies notably to Cryptorchism, Severe epilepsy, Severe knee and white coat color. These traits also show relatively small influences of litter effects and other risk factors on the estimate of heritability. Other traits have lower heritabilities and/or are clearly influenced by non-genetic effects, e.g. Cheilo and Epilepsy and Knee with a more liberal definition. In general these traits appear multifactorial and genetic counseling therefore is best based on models that allow inclusion of additional explaining effects and risk terms, such as the probit model applied here. This study also shows that data collection by questionnaires supplies data of sufficient quality for genetic counseling.

Acknowledgments
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References


53. Cameron ND. Selection indices and prediction of genetic merit in animal breeding. *Wallingford: CAB international, 1997*
Table 1: Number of cases, non-cases, prevalences and mortality in a birth cohort of 2629 boxers.

<table>
<thead>
<tr>
<th>Traits</th>
<th>Cases</th>
<th>Non-cases</th>
<th>Prevalence$^1$</th>
<th>Dead or euthanased</th>
<th>Mortality of cases (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cheilo</td>
<td>61</td>
<td>2561</td>
<td>2.3</td>
<td>61</td>
<td>100.0</td>
</tr>
<tr>
<td>Cryptorchism$^2$</td>
<td>80</td>
<td>667</td>
<td>10.7</td>
<td>0</td>
<td>0.0</td>
</tr>
<tr>
<td>Epilepsy</td>
<td>49</td>
<td>1984</td>
<td>2.4</td>
<td>20</td>
<td>40.8</td>
</tr>
<tr>
<td>Severe epilepsy</td>
<td>34</td>
<td>1984</td>
<td>1.7</td>
<td>19</td>
<td>55.8</td>
</tr>
<tr>
<td>Knee</td>
<td>117</td>
<td>1932</td>
<td>5.7</td>
<td>2</td>
<td>1.7</td>
</tr>
<tr>
<td>Severe knee</td>
<td>59</td>
<td>1933</td>
<td>3.0</td>
<td>1</td>
<td>1.7</td>
</tr>
<tr>
<td>Heart murmur</td>
<td>200</td>
<td>1852</td>
<td>9.7</td>
<td>22</td>
<td>11.0</td>
</tr>
<tr>
<td>Heart abnormalities</td>
<td>55</td>
<td>1852</td>
<td>2.9</td>
<td>9</td>
<td>16.4</td>
</tr>
<tr>
<td>Aortic stenosis</td>
<td>24</td>
<td>1852</td>
<td>1.3</td>
<td>10</td>
<td>41.7</td>
</tr>
<tr>
<td>White</td>
<td>227</td>
<td>2333</td>
<td>8.7</td>
<td>102</td>
<td>44.9</td>
</tr>
</tbody>
</table>

$^1$ Prevalence: Cases as a percentage of the non-cases plus cases. Boxers with missing data (e.g. a male dog that died during the first week) were excluded in this prevalence calculation.

$^2$ Prevalence was calculated using males exclusively.
<table>
<thead>
<tr>
<th>Traits</th>
<th>risk factor</th>
<th>$h^2$</th>
<th>$h^2$ (corrected for litter)$^2$</th>
<th>$h^2$ (corrected for litter and risk factors)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cheilo</td>
<td>-</td>
<td>0.27</td>
<td>0.17</td>
<td>n.a.$^3$</td>
</tr>
<tr>
<td>Cryptorchism</td>
<td>-</td>
<td>0.24</td>
<td>0.23</td>
<td>n.a.$^3$</td>
</tr>
<tr>
<td>Epilepsy</td>
<td>sex</td>
<td>0.11</td>
<td>0.01</td>
<td>0.08</td>
</tr>
<tr>
<td>Severe epilepsy</td>
<td>sex</td>
<td>0.36</td>
<td>0.34</td>
<td>0.33</td>
</tr>
<tr>
<td>Knee</td>
<td>adult weight</td>
<td>0.15</td>
<td>0.15</td>
<td>0.16</td>
</tr>
<tr>
<td>Severe knee</td>
<td>adult weight</td>
<td>0.28</td>
<td>0.27</td>
<td>0.28</td>
</tr>
<tr>
<td>Heart murmur</td>
<td>sex</td>
<td>0.04</td>
<td>0.00</td>
<td>0.00</td>
</tr>
<tr>
<td>Heart abnormalities</td>
<td>sex</td>
<td>0.01</td>
<td>0.00</td>
<td>0.00</td>
</tr>
<tr>
<td>Aortic stenosis</td>
<td>sex</td>
<td>0.00</td>
<td>0.00</td>
<td>0.00</td>
</tr>
<tr>
<td>White</td>
<td>-</td>
<td>0.61</td>
<td>n.a.$^3$</td>
<td>n.a.$^3$</td>
</tr>
<tr>
<td>Birth weight</td>
<td>sex, litter size</td>
<td>0.55</td>
<td>0.54</td>
<td>0.62</td>
</tr>
<tr>
<td>Adult weight</td>
<td>litter size, neutered height</td>
<td>0.18</td>
<td>0.08</td>
<td>0.04</td>
</tr>
<tr>
<td>Height</td>
<td>-</td>
<td>0.53</td>
<td>n.a.$^3$</td>
<td>n.a.$^3$</td>
</tr>
</tbody>
</table>

$^1$ Risk factors that are known from literature to be possibly related to a trait. The heritability is corrected for these risk factors in the last column (as fixed effect in the model).

$^2$ Dogs in one litter shared the same environment during gestation time and the first weeks of life. Less variance between litter mates than between dogs from different litters is to be expected. Therefore, heritability was corrected for litters (as random effect in the model).

$^3$ n.a.: Not analyzed, because there were no risk factors for these traits involved in this study.
Table 3. Heritability ($h^2$) of traits in a single gene-model in a birth cohort of 2629 boxers.

<table>
<thead>
<tr>
<th>Traits</th>
<th>$h^2$ total</th>
<th>SD</th>
<th>90% CI</th>
<th>$h^2$ additive</th>
<th>SD</th>
<th>90% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cheilo</td>
<td>0.17</td>
<td>0.10</td>
<td>0.00 - 0.59</td>
<td>0.09</td>
<td>0.09</td>
<td>0.00 - 0.55</td>
</tr>
<tr>
<td>Cryptorchism</td>
<td>0.22</td>
<td>0.14</td>
<td>0.00 - 0.74</td>
<td>0.11</td>
<td>0.09</td>
<td>0.00 - 0.53</td>
</tr>
<tr>
<td>Epilepsy</td>
<td>0.18</td>
<td>0.10</td>
<td>0.00 - 0.59</td>
<td>0.10</td>
<td>0.09</td>
<td>0.00 - 0.49</td>
</tr>
<tr>
<td>Severe epilepsy</td>
<td>0.21</td>
<td>0.10</td>
<td>0.02 - 0.61</td>
<td>0.14</td>
<td>0.11</td>
<td>0.00 - 0.57</td>
</tr>
<tr>
<td>Aortic stenosis</td>
<td>0.09</td>
<td>0.09</td>
<td>0.00 - 0.56</td>
<td>0.04</td>
<td>0.05</td>
<td>0.00 - 0.51</td>
</tr>
<tr>
<td>White</td>
<td>0.53</td>
<td>0.08</td>
<td>0.22 - 0.78</td>
<td>0.34</td>
<td>0.12</td>
<td>0.00 - 0.70</td>
</tr>
</tbody>
</table>

1 Heritability in the broad sense: the total genetic variance divided by the phenotypic variance.
2 Standard deviation.
3 Ninety percent confidence interval.
4 Heritability in the narrow sense: the additive genetic variance divided by the phenotypic variance.
Figure 1. Numbers of cases of the binomial traits in clusters of related boxers (relatedness >0.125). Each vertical line hitting the x-axis (0.125 relation coefficient) represents a cluster. The upper part of the y-axis represents the level of relatedness between clusters. In the lower part of the y-axis, the number of boxers per cluster, the number of cases per cluster and the total numbers of cases per trait (between brackets) are figured. Clusters with 95% confidence intervals of the RR with a minimum value higher than 1 or a maximum value lower than 1, were considered significantly different from the total population. (*: RR was significantly higher than 1, **: RR was significantly lower than 1).

1 To group the boxers into clusters of related dogs (relatedness > 0.125) a hierarchal cluster analysis was performed using the estimated genetic similarity of all pair-wise combined dogs.
Table 4. Correlation coefficients (r) of the prevalence of a trait per cluster and the average breeding value of this trait per cluster. The average breeding values were calculated in the probit models with and without correction for litter and risk factors.

<table>
<thead>
<tr>
<th>Traits</th>
<th>Corrected for litter</th>
<th>Corrected for litter and risk factors</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>r</td>
<td>r</td>
</tr>
<tr>
<td>Cheilo</td>
<td>0.735</td>
<td>0.718</td>
</tr>
<tr>
<td>Cryptorchism</td>
<td>-0.053</td>
<td>-0.052</td>
</tr>
<tr>
<td>Epilepsy</td>
<td>-0.168</td>
<td>-0.137</td>
</tr>
<tr>
<td>Severe epilepsy</td>
<td>0.839</td>
<td>0.837</td>
</tr>
<tr>
<td>Knee</td>
<td>0.466</td>
<td>0.464</td>
</tr>
<tr>
<td>Severe knee</td>
<td>0.745</td>
<td>0.740</td>
</tr>
<tr>
<td>Heart murmur</td>
<td>0.774</td>
<td>0.716</td>
</tr>
<tr>
<td>Heart abnormalities</td>
<td>0.727</td>
<td>0.724</td>
</tr>
<tr>
<td>Aortic stenosis</td>
<td>0.747</td>
<td>0.750</td>
</tr>
<tr>
<td>White</td>
<td>0.813</td>
<td>0.730</td>
</tr>
</tbody>
</table>

¹ n.a.: Not analyzed, because there were no risk factors for these traits involved in this study.
Figure 2. Scatter plots of prevalence and average breeding values in clusters. To group the boxers into clusters of related dogs (relatedness > 0.125) a hierarchal cluster analysis was performed using the estimated genetic similarity of all pair-wise combined dogs. Plots of the traits White, Cryptorchism, Epilepsy and Knee were figured as example for high, average and low correlations.