SEGREGATION ANALYSIS FOR HIP AND EL BOW DYSPLASIA IN THE FINNISH ROTTWEILER

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INTRODUCTION

Canine hip and elbow dysplasia have been reported as quantitative traits (e.g. Leighton *et al.*, 1977 ; Swenson *et al.*, 1997). In addition to the quantitative inheritance, a possibility of a major gene or mitochondrial inheritance has been suggested (e.g. Janss and Brascamp, 1998 ; Todhunter *et al.*, 1999). Mäki *et al.* (2002) studied the mode of inheritance in four Finnish dog populations. Existence of segregating major genes was preliminarily assessed based on frequency distributions of hip and elbow dysplasia of the offspring of individual sires. These family specific distributions did not show any sign of major genes, for example multimodality. This does not, however, rule out the possibility of a major gene in either of the traits, as the effect of a major gene would have to be very large to affect the distributions of the traits. In this study a segregation analysis was applied in order to assess the possible existence of major genes affecting hip and/or elbow dysplasia in the Finnish Rottweiler population.

MATERIAL AND METHODS

Material. Pedigree information and radiographic results of the Rottweilers screened for hip (HD) and elbow dysplasia (ED) during the years 1988 to 2000 were obtained from the Finnish Kennel Club. HD classification had been changed twice during the time the data covered. The three sets of grades were combined to form the classes 1 and 1.5 (normal), 2 (borderline), 3 (mild), 4 (moderate), and 5.0, 5.5, and 6.0 (severe). Classes 1.5, 5.0 and 6.0 consisted of only old records, whilst in other classes both old records and records graded according to the current system existed. ED had been classified according to International Elbow Working Group protocol, from normal or borderline to severe dysplasia (0 to 3). The data included 4 397 HD and 3 386 ED records, and the pedigree in the statistical analyses included 13 729 dogs. Incidences of HD and ED in the data were 32 % and 46 %, respectively.

Segregation analysis may be sensitive to deviations from normality not caused by a single gene (Lynch and Walsh, 1998). The distributions of HD and ED in these data were skewed, and the distribution of HD records was bimodal because the grades of all three classification systems were combined. Furthermore, the distribution is even more complicated if the mean of the left and the right joints is taken as a studied trait like it was in this study, with 15 possible values for hip and 7 classes for elbow joints (HD and ED). This is because often left and right joint

are not similarly affected. In addition to HD and ED, the grades of only the left joint of each dog (HDL and EDL) were analysed. For HDL, only the grades of the present Fédération Cynologique Internationale classification (n = 4 129) were used to prevent the 'false' bimodal distribution.

Genetic models. First, polygenic animal models, assuming additive gene effects, were applied. The models included age, sex, year of birth and panelist (radiologist) as fixed effects, and breeder, litter and additive genetic effect of an animal as random effects. Effect of a major gene was added to the polygenic model when presence of possible major genes was analysed:

$$\mathbf{y = X1ß + X2b + X3c + Zu + ZWm + e,}$$

where **y** = grades for HD or ED, **ß** = non-genetic fixed effects, **b** = random breeder effects, **c** = random litter effects, **u** = additive genetic effects, **W** = genotypes, **m** = genotype means, and **e** = random errors. **X1, X2, X3** and **Z** were incidence matrices relating non-genetic and genetic effects to the observations. The distributions of **b**, **c**, **u** and **e** were assumed to be $\mathbf{b}\sim N(0,\mathbf{I}\sigma_b^2)$, $\mathbf{c}\sim N(0,\mathbf{I}\sigma_c^2)$, $\mathbf{u}\sim N(0,\mathbf{A}\sigma_u^2)$ and $\mathbf{e}\sim N(0,\mathbf{I}\sigma_e^2)$. Prior distributions were defined as $(-\infty,\infty)$ for the non-genetic effects and effects at the single locus, as $(0,\infty)$ for the variance components, and as (0,1) for the allele frequencies. The major gene was modelled as an autosomal bi-allelic locus with Mendelian transmission probabilities. The alleles at the major locus were defined as A1, the allele that decreases the value of phenotypic measurements, and A2, the allele that increases it. Matrix **W** is a four-column matrix indicating the genotype of each animal: A1A1, A1A2, A2A1, or A2A2. Effects of the genotypes are in **m**, with $\mathbf{m}' = (-a, d, d, a)$, where *a* is referred to as the additive and *d* as the dominant effect at the major gene locus.

Computing procedure. Detection of major genes was based on a Bayesian modelling approach to segregation analysis (Janss *et al.,* 1995). Computations were performed by a Monte Carlo Markov Chain algorithm (magic ; Janss, 1998). For polygenic models, five Gibbs chains were run per trait, each of 25 500 cycles including a burn-in period of 500. Samples of model parameters were written out every 50th cycle, resulting in 500 samples per chain. Five chains per trait were run for the mixed models as well, each of 40500 cycles. Evaluation of the burn-in period and computing of the mean and standard deviation of the posterior distribution were done with Gibanal (van Kaam, 1998). Convergence of the Gibbs sampler was determined by plotting a parameter value versus cycle number. Non-parametric density estimates of posteriors were made according to the average shifted histograms (Scott, 1992).
Major gene variance (σ_w^2) was computed from genotype frequencies and the genotypic effects *a* and *d* in each Gibbs sample as $2pq(a+d(q-p))^2+(2pqd)^2$ (Falconer and Mackay, 1996), where *p* is the frequency of the unfavourable A2 allele and $q=1-p$. Non-significance of a variance component is shown to lead to a posterior distribution with a global mode of zero (Janss *et al.*, 1995), whereas significance of the variance component shows a global mode greater than zero. The σ_w^2 was accepted to be significant only when a global mode for $\sigma_w^2>0$ had a 20-fold larger density compared to the density at $\sigma_w^2=0$.

RESULTS AND DISCUSSION

For both HD and ED, a significant major gene variance was detected (figure 1). When going from the polygenic models to the mixed inheritance models, polygenic variation (σ_u^2) diminished, yet remaining still significant in both traits (table 1). Compared to HD and ED, polygenic variation was even smaller for HDL and EDL, and, for ED, the major gene variance was smaller than for EDL. This is probably because the complicated distributions of HD and ED suggest larger influence of polygenes and environment on the traits, compared to the more straightforward distributions of HDL and EDL.

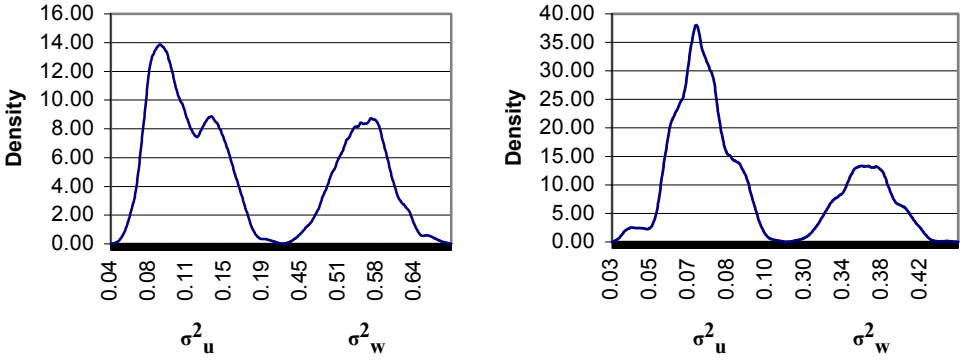

Figure 1. Polygenic (σ^2_u) and major gene (σ^2_w) variance for hip and elbow dysplasia, respectively

Table 1. Estimates of marginal posterior means and standard deviations (in brackets) for polygenic (σ^2_u), major gene (σ^2_w), breeder (σ^2_b), litter (σ^2_c) and residual (σ^2_e) variance

Trait	σ^2_u	σ^2_w	σ^2_b	σ^2_c	σ^2_e
HD-poly[A]	0.43 (0.08)	-	0.08 (0.02)	0.05 (0.02)	0.65 (0.04)
HD[B]	0.10 (0.03)	0.55 (0.05)	0.03 (0.01)	0.03 (0.01)	0.29 (0.02)
HDL[C]	0.05 (0.01)	0.57 (0.05)	0.01 (0.01)	0.03 (0.01)	0.27 (0.01)
ED-poly[A]	0.18 (0.03)	-	0.01 (0.00)	0.02 (0.01)	0.27 (0.02)
ED[B]	0.07 (0.01)	0.36 (0.03)	0.01 (0.00)	0.01 (0.01)	0.15 (0.01)
EDL[C]	0.04 (0.01)	0.44 (0.03)	0.01 (0.00)	0.01 (0.00)	0.23 (0.02)

[A]poly = polygenic model ; [B]HD, ED = hip and elbow dysplasia ; mixed inheritance model ; mean of the left and the right joint ; [C]HDL, EDL = hip and elbow dysplasia ; mixed inheritance model ; left joint

Allele effects at the major gene loci revealed close to complete dominance in both traits, with the favourable allele A1 being dominant (table 2). The allele effects were quite large, approximately two phenotypic standard deviations in both traits. This size of an effect could be visible even in the phenotypic distribution of a trait. The distribution would be platykurtic when the allele frequencies are intermediate (Lynch and Walsh, 1998) as in this study, but this cannot be seen in the distributions of HD and ED (Mäki *et al*., 2002). High frequencies of the

unfavourable recessive alleles, especially in hip dysplasia, suggest that it is possible to gain considerable genetic progress in both traits by selection on the major genes. So far genetic progress, based on phenotypic selection, has been very small (Mäki *et al*., 2002). In a study of Todhunter *et al*. (1999), two dominant major genes were reported to affect HD. For our data, further analysis is required to study potential biases from non-normality and to further validate the existence of major genes.

Table 2. Estimates of marginal posterior means and standard deviations (in brackets) for allele effects (a and d) and for the frequency of the favourable A1 allele (Fr(A1))

Trait	*a*	*D*	Fr(A1)
HD[A]	0.91 (0.04)	-1.00 (0.06)	0.38 (0.05)
HDL[B]	0.99 (0.03)	-0.92 (0.06)	0.38 (0.05)
ED[A]	0.66 (0.02)	-0.64 (0.04)	0.58 (0.05)
EDL[B]	0.75 (0.03)	-0.69 (0.04)	0.59 (0.05)

[A]HD, ED = hip and elbow dysplasia ; mixed inheritance model ; mean of the left and the right joint ; [B]HDL, EDL = hip and elbow dysplasia ; mixed inheritance model, left joint

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