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ORIGINAL ARTICLE

Genetic analyses of elbow and hip dysplasia in the German shepherd dog

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Summary

Results from radiographic screening for canine hip dysplasia (CHD) and elbow dysplasia (CED) of 48 367 German shepherd dogs born in 2001–07 were used for the population genetic analyses. Available information included CHD scores for 47 730 dogs, CED scores for 28 011 dogs and detailed veterinary diagnoses of primary ED lesions for a subsample of 18 899 dogs. Quasi-continuous traits were CHD, CED and cases of CED without radiographically visible primary lesion (CED-ARTH). Binary coding was used for fragmented medial coronoid process of the ulna (FCP), borderline findings and mild to severe signs of dysplasia in hip and elbow joints. Genetic parameters were estimated in univariate threshold and multivariate linear and mixed linear-threshold models using Gibbs sampling. Correlations between univariately predicted breeding values (BV) indicated genetic differences between borderline and affected disease status for both CHD ($r_{BV} = 0.5$) and CED ($r_{BV} = 0.3$). Multivariate genetic analyses with separate consideration of borderline findings revealed moderate heritabilities of 0.2–0.3 for the quasi-continuous traits with positive additive genetic correlation of 0.3 between CHD and both CED and CED-ARTH. For FCP, heritability of 0.6 and additive genetic correlations of +0.1 to CHD and −0.1 to CED-ARTH were estimated. Results supported the relevant genetic determination of CHD and CED, argued for both diseases against interpretation of borderline findings as healthy and implied genetic heterogeneity of CED. Accordingly, future breeding strategies to reduce the prevalences of CHD and CED in the German shepherd dog should be most efficient when based on BV from multivariate genetic evaluation for CHD, CED-ARTH and FCP with use of the whole scale of categories for classification of CHD and CED.

Introduction

Locomotory diseases are of great concern for all dog breeds as they do not only interfere with the use of working and sport dogs, but compromise the welfare of affected dogs. Many studies showed heritabilities around 0.2 for canine hip dysplasia (CHD) and canine elbow dysplasia (CED) for a large number of dog breeds (e.g. Hedhammar *et al.* 1979; Lingaas & Klemetsdal 1990; Grøndalen & Lingaas 1991; Swenson *et al.* 1997; Beuing *et al.* 2000; Mäki *et al.*, 2001; Dietschi *et al.* 2003; Hamann *et al.* 2003; Janutta *et al.* 2006). Subsequent breeding measures to reduce CHD and CED prevalences were mostly based on disease phenotypes, i.e. classification based on the radiographs of the respective joints. More recently,

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breeding values (BV) obtained by best linear unbiased prediction have been used to complement selection programmes, particularly with respect to CHD.

To explain the genetic background of polygenic traits, the liability concept postulates some underlying, normally distributed continuous variable called liability. This concept implies that signs of disease will be visible when liability to the respective disease has exceeded a certain threshold. In dysplastic hip and elbow joints, radiographically visible signs vary from localized and subtle to extensive and severe, and scores with multiple levels are used to reflect this phenotypic variation. Such scoring captures more information than sole distinction between healthy and diseased and facilitates inferring individual disease liabilities, which is the aim of genetic evaluation.

In the German population of German shepherd dogs (GSD), mass selection against CHD had been supported by planning of matings based on genetic evaluation since 1999. Although there was some success in reducing the proportions of severely affected dogs, improvement slowed down implying necessary adjustment of selection strategies (Janutta & Distl 2008). Obligatory CED screening- and phenotype-based breeding restrictions have been introduced in the GSD in 2002, so effects of these measures have not yet been reported. Given the extension rather than replacement of actions for improving the locomotory health in the GSD, correlations between all now considered conditions should be taken into account to allow for optimum multi-trait selection. Along with the CED scores, detailed veterinary diagnoses for fragmented medial coronoid process of the ulna (FCP), ununited anconeal process (UAP) and osteochondrosis or osteochondrosis dissecans of the medial humeral condyle (OCD) were recorded. Because FCP had a prevalence of approximately 4%, we distinguished among CED cases only showing arthroses (CED-ARTH) and dogs showing FCP with or without accompanying arthroses. Accordingly, the aim of this study was to estimate the genetic correlations between CHD and CED as currently recorded by the breeding organization and among CHD, CED-ARTH and FCP.

There is considerable controversy about the relevance of certain radiographic findings in hip and elbow joints for the dogs' health. Classification as borderline has been introduced to express that the respective joints are neither completely free from abnormalities nor clearly dysplastic. Borderline CHD and CED do usually not entail any breeding restrictions, but there is no scientific justification for this practice. Therefore, a further aim of this study was to perform genetic correlation analyses with special focus on the dogs diagnosed as borderline and the genetic correlation between borderline and dysplastic hip and elbow joints.

Material and methods

Radiographic data

Radiographic examination data of GSD, registered by the German breeding association for GSD (Verein für Deutsche Schäferhunde e.V., SV), were used for this study. Available information referred to evaluation results of hip joints with respect to hip dysplasia (CHD) and of elbow joints with respect to elbow dysplasia (CED). Joint assessments were made according to the rules of the Fédération Cynologique International (FCI) and the regulations of the Association for Radiological Diagnosis of Genetically Influenced Skeletal Diseases in small animals (Gesellschaft für Röntgendiagnostik genetisch beeinflusster Skeletterkrankungen bei Kleintieren; http://www.grsk.org) for the hip joint and the International Elbow Working Group (IEWG; http://www.iewg-vet.org/) for the elbow joint. According to the IEWG, dogs are considered affected by CED when showing at least one of the following findings: elbow joint arthroses; FCP; UAP; osteochondrosis or OCD.

Canine hip dysplasia and CED were both scored on separate five-point scales distinguishing between dogs free of radiological signs of the respective disease (CHD-A, CED-0), dogs with radiographic findings of uncertain disease relevance (near normal or 'borderline'; CHD-B, CED-1) and dogs with mild to severe radiological signs of the respective disease (CHD-C to E, CED-2 to 4). In case of different severity of radiologically visible alterations in left and right joints, the worse side determined the final classification of the individual with respect to CHD and CED. Evaluation of CHD and CED scores was performed by one veterinary expert each and made available for this study by the SV. Details on locations and extent of elbow joint alterations and on FCP, UAP and OCD were provided by the radiological expert responsible for CED assessment under the SV. For the statistical analysis, the official CHD scores ranging from A to E were transformed to a corresponding numerical scale ranging from one to five.

Whilst radiographic screening for CHD had already been introduced by the SV as early as 1966, examination for CED had become obligatory not before

Table 1 Distribution of the 48.367 dogs from the German population of German shepherd dogs from birth years 2001–07 which were included in the study because of known status with respect to hip dysplasia (CHD) or elbow dysplasia (CED)

	Numbers of dogs with disease information (males/females; first line), means and SDs for examination age (second line) and disease score (scale 1–5 for CHD, scale 0–4 for CED; third line)		
Year of birth	CHD	CED	CHD or CED
2001	7595 (3676/3919)	1707 (901/806)	7611 (3687/3924)
	14.89 ± 5.28	17.52 ± 10.70	
	1.50 ± 0.77	1.85 ± 0.82	
2002	7804 (3838/3966)	2003 (1061/942)	7826 (3847/3979)
	14.75 ± 5.24	18.35 ± 10.63	
	1.50 ± 0.78	1.84 ± 0.93	
2003	7251 (3483/3768)	2616 (1290/1326)	7296 (3503/3793)
	14.95 ± 5.35	19.25 ± 10.19	
	1.49 ± 0.76	1.72 ± 0.87	
2004	7165 (3428/3737)	5198 (2277/2921)	7245 (3458/3787)
	14.95 ± 4.88	18.60 ± 9.11	
	1.46 ± 0.73	1.89 ± 0.95	
2005	6639 (3171/3468)	5873 (2755/3118)	6816 (3241/3575)
	14.82 ± 4.40	15.68 ± 5.66	
	1.46 ± 0.74	1.89 ± 0.96	
2006	6082 (2808/3274)	5705 (2603/3102)	6331 (2903/3428)
	14.38 ± 3.31	14.93 ± 3.85	
	1.38 ± 0.69	1.96 ± 0.96	
2007	5194 (2440/2754)	4909 (2296/2613)	5242 (2458/2784)
	13.47 ± 1.84	13.68 ± 2.13	
	1.30 ± 0.63	2.08 ± 1.01	
2001–07	47 730 (22 844/24 886)	28 011 (13 183/14 828)	48 367 (23 097/25 270)
	14.65 ± 4.64	16.54 ± 7.70	
	1.45 ± 0.74	1.91 ± 0.95	

2002. Given the minimum age of 12 month for radiological examination for both hip and elbow joints, more than 95% of available CED information referred to dogs born between 2001 and 2007. Although the CHD data set included dogs as of birth year 1980, only dogs with regular CED information and their contemporaries were considered for this study. Further inclusion criteria were known examiner and known examination age of at least 12 months for the respective diseases. These requirements were fulfilled by 48 367 dogs including 23 097 males and 25 270 females from birth years 2001 to 2007. The number of dogs with known disease status was 47 730 for CHD and 28 011 for CED. The distribution of dogs with CHD or CED information by year of birth is given in Table 1. Data were generally available for slightly more female than male dogs, with a male to female ratio mostly ranging between 1 : 1.1–1.2. Most of the dogs were radiologically examined soon after having passed the minimum age of 12 months: 89% of the CHD data and 80% of the CED data were collected at 12–18 months of age. Of the 47 730 dogs with information on CHD, 66.6% did not show any signs of CHD (CHD-A), 24.9% were classified as near normal with regard to CHD (CHD-B) and 8.5% as slightly to severely affected by CHD (6.2% CHD-C, 1.9% CHD-D, 0.5% CHD-E). Of the 28 011 dogs with information on CED, 83.9% did not show any signs of CED (CED-0), 6.7% were classified as borderline with regard to CED (CED-1) and 9.3% as slightly to severely affected by CED (5.4% CED-2, 2.6% CED-3, 1.3% CED-4).

To enable comparative analyses of the findings of uncertain and clear disease relevance, two distinct binary traits per disease were defined: for CHD, CHD_bord (1 = classified as CHD-B, 0 = classified as CHD-A, missing values for dogs classified as CHD-C to E) and CHD_aff (1 = classified as CHD-C to E, 0 = classified as CHD-A, missing values for dogs classified as CHD-B); for CED, CED_bord (1 = classified as CED-1, 0 = classified as CED-0, missing values for dogs classified as CED-2 to 4) and CED_aff (1 = classified as CED-2 to 4, 0 = classified as CED-0, missing values for dogs classified as CED-1). Introduction of the missing values ensured that findings of uncertain and clear disease relevance were treated as separate types of diseases, sharing the same reference of healthy joints. This procedure was justified by the fact that genetic effects are not the only reasons for

observed phenotypic variation and genetic variation exists within each category of CHD and CED phenotype. Therefore, ignorance of certain phenotype categories did not interfere with the basic assumption of approximate normal distribution of the underlying liability in each of the analyses performed (CHD_bord, CHD_aff, CED_bord, CED_aff).

Details of the radiographic findings in the elbow joints were documented for 18 899 of the dogs. IEWG definition of CED includes cases with and without visible primary lesions (specific joint diseases FCP, UAP, OCD). Because of the possibly differing etiopathology of the different forms of CED, radiological details were used to identify dogs which were classified as CED borderline or affected without showing indications of a specific elbow disease (CED diagnosis based on arthroses, CED-ARTH). The specific elbow joint diseases were rarely found, UAP in 0.6%, OCD in 0.1% and FCP in 4.4% of the dogs, so only FCP was separately included in the genetic analyses.

Genetic analyses

Model development was based on the results of multiple analyses of variance using the procedure MIXED of the software package Statistical Analysis System (SAS), Version 9.2 (SAS Institute Inc., Cary, NC, USA 2009). Here, sex (male, female), year of birth (individual years from 2001 to 2007) and season of birth (January–March, April–June, July–September, October–December) were considered as fixed effects. Age at radiological examination was either considered as covariate (linear; linear and quadratic; linear, quadratic and logarithmic; linear, quadratic, logarithmic and logarithmic-quadratic) or as fixed effect (12–18 months, >18 months). Model comparison further included the random effects of the veterinarian having taken the radiographs and of kennel, dam or litter.

To study the effects of different modelling on the estimates of genetic parameters, preliminary analyses were performed for CHD and CED using different models and residual maximum likelihood (REML) with the program Variance Component Estimation, Version 5.1.2 (Institute of Farm Animal Genetics, Friedrich Loeffler Institute (FLI), Mariensee, Germany) (Kovač *et al.* 2003). As in all subsequent analyses, pedigree information on up to eight generations was considered, resulting in a total size of the relationship matrix of 82 316 animals. The effect of the model choice on the parameter estimates was in most cases negligible. Despite significance in the analysis of variance, variances between kennels and veterinarians were found to be very small, and genetic parameter estimates were only marginally affected by their inclusion or non-inclusion in the model. This applied to both the quasi-continuous traits (CHD, CED, CED-ARTH) and the binary traits (CHD_bord, CHD_aff, CED_bord, CED_aff). Therefore, random effects other than the additive genetic effect of the animal were not included in the final model which was identical for all traits: $y_{ijklmn} = \mu + \mathrm{SEX}_i + \mathrm{YEAR}_j + \mathrm{SEASON}_k + \mathrm{AGE}_l + a_m + e_{ijklmn}$ with y_{ijklmn} = radiographic finding in the hip joints (CHD_bord, CHD_aff; CHD) or elbow joints (CED_bord, CED_aff; CED, CED-ARTH), μ = model constant, SEX_i = fixed effect of the ith sex (i = 1–2), YEAR_j = fixed effect of the jth year of birth (j = 1–7), SEASON_k = fixed effect of the kth season of birth (k = 1–4), AGE_l = fixed effect of the lth class of examination age (l = 1–2), a_m = random additive genetic effects of the mth individual (m = 1–82 316), and e_{ijklmn} = random residual.

Because of the previously found higher accuracy of Gibbs sampling (GS) when compared to REML (Stock *et al.* 2007) and the possibility to perform threshold and mixed linear-threshold model analyses, GS was used for the definite genetic analyses. Genetic parameters were estimated in univariate threshold animal models for all binary traits, in multivariate linear animal models for the quasi-continuous traits CHD and CED and in multivariate linear-threshold animal models for the quasi-continuous traits CHD and CED-ARTH and the binary trait FCP with the threshold version of the Multiple Trait Gibbs Sampler for Animal Models (Van Tassell & Van Vleck 1996). The starting values chosen were one for the additive genetic and the residual variances. In the multivariate analyses, the starting value for the additive genetic covariances was zero, and the residual covariances were fixed to zero. To express little prior knowledge and at the same time assure posterior propriety, a proper prior following an inverted Wishart distribution with minimum shape parameter ($\nu_{\mathrm{IW}} = \mathrm{n} + 2$ for multivariate analyses of n traits, so $\nu_{\mathrm{IW}(1)} = 4$ and $\nu_{\mathrm{IW}(2)} = 5$) was adopted for the genetic (co)variance matrix. A flat prior was used for the fixed effects. In each case, the total length of the Gibbs chain was set to 205 000 rounds, with the first 5000 rounds being afterwards discarded as burn-in. Sufficiency of the length of burn-in was assured, and convergence of the Gibbs chain was assessed by visual inspection of the sample plots. Posterior means of additive genetic and residual (co)variance, heritabilities and additive

genetic correlations were calculated from unthinned chains of postconvergence samples.

Univariate prediction of BV for the four binary traits CHD_bord, CHD_aff, CED_bord and CED_aff was followed by the estimation of Pearson correlation coefficients between the BV within disease, using the procedure CORR of SAS. To account for different reliability of genetic evaluation, BV correlations were estimated in all dogs and in breeding animals with radiologically examined offspring.

To facilitate the comparison between the BV, they were subsequently standardized to a mean of 100 and a SD of 20. Herein, all dogs classified as free of the respective condition (dogs with CHD-A for CHD_bord and CHD_aff; dogs with CED-0 for CED_bord and CED_aff) served as reference population. Standardization was performed in such way that relative breeding values (RBV) larger than 100 indicate above-average and RBV smaller than 100 indicate below-average likelihood to pass the disposition for the respective trait to the offspring. For example, a RBV of 120 for CED_bord stands for a tendency to have offspring showing radiographic signs of borderline CED, whilst a RBV of 120 for CED_aff stands for an expected high proportion of CED grades 2–4 among the offspring. RBV plots by the CHD and CED phenotype were used to illustrate similarities and dissimilarities of the univariate genetic evaluations for the binary traits (RBV for CHD_bord versus CHD_aff and CED_bord versus CED_aff). RBV distributions were investigated within disease category (free, borderline, affected) for CHD and CED using the procedure UNIVARIATE of SAS. The relationship between phenotypes and RBV further was analysed by simple analyses of variance using the procedure GLM of SAS. In that, RBV for CHD_bord, CHD_aff, CED_bord and CED_aff were considered as dependent variables, and status of the respective disease was considered as independent variable. The significance limit was set to $p = 0.05$.

Results

The sample plots of the initial univariate analyses indicated good mixing and fast convergence of the Gibbs chains for all traits. Convergence was in all cases achieved within the first 5000 rounds. Posterior means of variance components revealed less genetic variation and lower heritabilities for the findings of uncertain disease relevance ($h^2 = 0.25 \pm 0.02$ for CHD_bord; $h^2 = 0.29 \pm 0.04$ for CED_bord) than for the findings of clear disease relevance ($h^2 = 0.43 \pm 0.03$ for CHD_aff; $h^2 = 0.56 \pm 0.04$ for CED_aff).

Pearson correlation coefficients between the univariately predicted BV are given in Table 2. The results for all dogs for which BV could be predicted were almost identical with those for the subsample of dogs with informative offspring. For both diseases considered, significantly positive correlations were determined within disease, i.e. between BV for the findings of uncertain and clear disease relevance ($p < 0.001$). Herein, CHD_bord was consistently closer correlated with CHD_aff ($r = 0.53$ in all dogs and $r = 0.54$ in parents of informants) than CED_bord with CED_aff ($r = 0.34$ in all dogs, 0.32 in parents of informants). BV correlations between diseases (CHD_bord and CED_bord, CHD_bord and CED_aff, CHD_aff and CED_bord, CHD_aff and CED_aff) were much lower, ranging between −0.07 and 0.04 ($p < 0.10$). The joint distributions of RBV predicted for findings of uncertain and clear disease status in the parents of informants are illustrated in Supplementary Figures S1 (CHD_bord and CHD_aff) and S2 (CED_bord and CED_aff).

The distributions of the univariately predicted RBV by the respective disease phenotypes are shown

Table 2 Pearson correlation coefficients (*r*) with their error probabilities (p) estimated between breeding values from univariate genetic evaluations for binary coded borderline and affected disease status with regard to hip dysplasia (CHD) and elbow dysplasia (CED) in German shepherd dogs

Population sample disease status	CHD_bord	CHD_aff	CED_bord	CED_aff
All dogs (n = 82 316)				
CHD_bord	–	0.529 (p < 0.001)	−0.071 (p < 0.001)	0.017 (p < 0.001)
CHD_aff		–	0.010 (p = 0.004)	0.044 (p < 0.001)
CED_bord			–	0.344 (p < 0.001)
CED_aff				–
Parents of dogs with known CHD or CED status (n = 16 580)				
CHD_bord	–	0.537 (p < 0.001)	−0.062 (p < 0.001)	0.021 (p = 0.008)
CHD_aff		–	0.013 (p = 0.094)	0.030 (p < 0.001)
CED_bord			–	0.318 (p < 0.001)
CED_aff				–

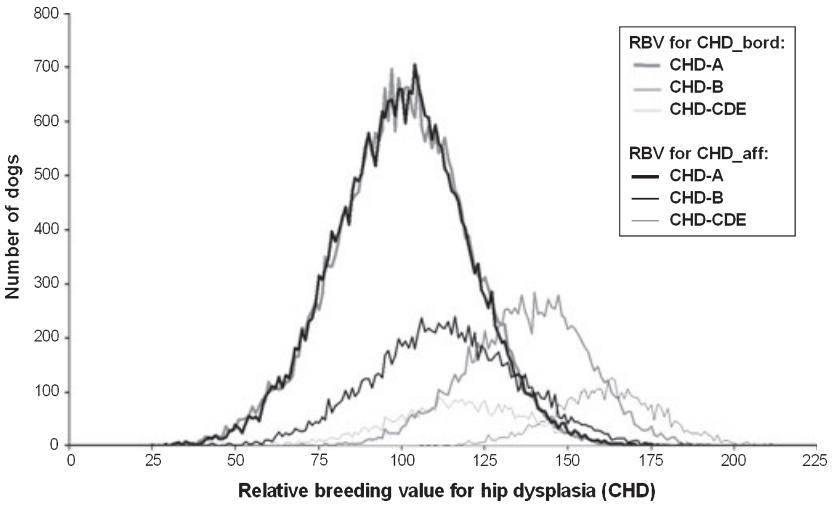

Figure 1 Distribution of univariately predicted relative breeding values (RBV) for disease status borderline and affected with respect to hip dysplasia (CHD_bord, CHD_aff), by the corresponding disease phenotype (CHD grade A, B and C to E) in 47,730 German shepherd dogs.

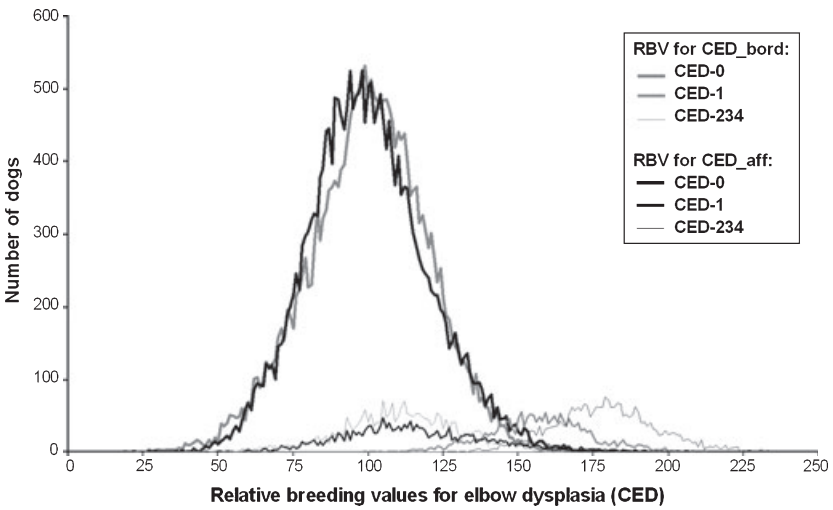

Figure 2 Distribution of univariately predicted relative breeding values (RBV) for disease status borderline and affected with respect to elbow dysplasia (CED_bord, CED_aff), by the corresponding disease phenotype (CED grade 0, 1 and 2 to 4) in 28,011 German shepherd dogs.

in Figures 1 and 2. In addition, the results of the corresponding simple analyses of variance are together with mean, median, minimum and maximum RBV given in Table 3. Within each of the three phenotype categories per disease (free, i.e. CHD-A or CED-0; borderline, i.e. CHD-B or CED-1; affected, i.e. CHD-C to E or CED-2 to 4), shapes of RBV distributions were similar with skewness values ranging from −0.21 to 0.06 for CHD_bord, CHD_aff and CED_bord, and from 0.09 to 0.37 for CED_aff. However, RBV means differed significantly between phenotype categories ($p < 0.001$). For both CHD and CED, differences between RBV means by phenotype category were larger for RBV for affected status (CHD_aff, CED_aff) than for RBV for respective borderline status (CHD_bord, CED_bord), supporting the current interpretation of greater similarity between free and borderline than between free and affected. Although there was considerable overlap between ranges of RBV, RBV predicted for affected disease status (CHD_aff, CED_aff) allowed distinction between disease phenotypes with means increasing from free over borderline to affected disease status for CHD (100.00 in dogs with CHD-A, 113.00 in dogs with CHD-B, and 161.83 in dogs with CHD-C to E) and CED (100.00 in dogs with CED-0, 114.81 in dogs with CED-1, and 179.11 in dogs with CED-2 to 4). RBV predicted for borderline disease status (CHD_bord, CED_bord) were on average lower in dogs free of the respective disease, but reflected the official scoring system considerably better for CHD than for CED.

Visual inspection of sample plots from the multivariate analyses indicated good mixing and fast convergence of the Gibbs chains, particularly for the parameters referring to the continuous traits. Discarding of the first 5000 rounds was sufficient to obtain postconvergence samples. The multivariately

Table 3 Means, medians and ranges (min–max) of univariately predicted relative breeding values (RBV) for borderline status (RBV_{CHD_bord}, RBV_{CED_bord}) and affected status (RBV_{CHD_aff}, RBV_{CED_aff}) with regard to hip dysplasia (CHD) and elbow dysplasia (CED) by phenotype of the respective disease

	Phenotype			p_{Diff}		
Disease and RBV	Free, i.e. CHD-A or CED-0	Borderline, i.e. CHD-B or CED-1	Affected, i.e. CHD-C to E or CED-2 to 4	Free – bord	Free – aff	Bord – aff
Hip dysplasia						
RBV_{CHD_bord}						
Mean	100.00	137.53	117.54	<0.001	<0.001	<0.001
Median	100	138	118			
Range	27–180	65–194	43–188			
RBV_{CHD_aff}						
Mean	100.00	113.00	161.83	<0.001	<0.001	<0.001
Median	100	113	162			
Range	25–189	31–210	106–215			
Elbow dysplasia						
RBV_{CED_bord}						
Mean	100.00	157.08	110.88	<0.001	<0.001	<0.001
Median	101	157	111			
Range	19–179	99–212	23–183			
RBV_{CED_aff}						
Mean	100.00	114.81	179.11	<0.001	<0.001	<0.001
Median	99	113	179			
Range	22–227	46–206	68–250			

Table 4 Heritabilities (on the diagonal) and additive genetic correlations (above the diagonal) with their SE estimated for canine hip dysplasia (CHD) and elbow dysplasia (CED) in a sample of 48 367 German shepherd dogs from birth years 2001 to 2007

	CHD	CED
CHD	0.254 ± 0.013	0.298 ± 0.026
CED		0.306 ± 0.018

Table 5 Heritabilities (on the diagonal) and additive genetic correlations (above the diagonal) with their SE estimated for canine hip dysplasia (CHD), elbow dysplasia (CED) without indications for a specific elbow disease (unspecific CED, CED-ARTH) and fragmented coronoid process of the ulna (FCP) in a sample of 48 367 German shepherd dogs from birth years 2001 to 2007

	CHD	CED-ARTH	FCP
CHD	0.252 ± 0.014	0.287 ± 0.031	0.143 ± 0.052
CED-ARTH		0.237 ± 0.018	−0.126 ± 0.068
FCP			0.568 ± 0.069

estimated genetic parameters are given in Tables 4 and 5. Moderate heritabilities, ranging between 0.24 and 0.31 (SE < 0.02), were estimated for CHD, CED and CED-ARTH. The heritability estimate for the binary trait FCP was higher, 0.57 (SE 0.07). Positive additive genetic correlation estimates were obtained between CHD on the one hand and CED, CED-ARTH and FCP on the other hand. However, CED and CED-ARTH were closer genetically correlated with CHD (r_g = 0.29–0.30, SE 0.03) than was FCP (r_g = 0.14, SE 0.05). The estimate for the additive genetic correlation between CED-ARTH and FCP was low and negative, −0.13 (SE 0.07).

Discussion

Several different classification schemes for CHD have been used with variation between countries and over time. Data for this study were collected according to the FCI protocol which distinguishes between five CHD grades; three of which (CHD grades C–E) clearly indicate CHD affection. Their combined prevalences should therefore provide a suitable basis for comparison of CHD affection rates. However, the reported proportions of CHD-affected dogs in different populations of GSD vary widely. Figures mentioned in recent literature were low for Germany (12.6%; Hamann *et al.* 2003), intermediate for Belgium (23%; Coopman *et al.* 2008) and France (22.1%; Genevois *et al.* 2007) and high for Finland (38.5%; Mäki *et al.* 2001). With 8.5% the proportion of dogs with CHD grades C–E was still well below the previously determined CHD affection rate in the

German population of GSD, but it is in line with the favourable genetic trend that has been documented (Janutta *et al.* 2008).

Concerning the phenotype-related breeding measures against CHD, findings leading to classification as CHD grade B are usually considered acceptable for breeding animals. The uncertain relevance for the individual dog, as for his progeny, has been the reason that breeding organizations refrained from imposing breeding bans or restrictions of breeding use for these dogs. Information on the meaning of the CHD grade B from a genetic point of view has not been previously reported. Here, we showed the genetic similarity between CHD grade B and CHD grades C–E, i.e. findings of clear disease relevance. In our separate analyses of CHD-bord, i.e. CHD grade B versus CHD grade A, and CHD_aff, i.e. CHD grades C to E versus CHD grade A, healthy dogs (CHD grade A) served as reference for standardization, and phenotypes of different parts of the study population were ignored (CHD grades C to E in the CHD_bord analyses, CHD grade B in the CHD_aff analyses). Although results were affected by regression of BV to the mean for dogs with 'unknown' phenotype, differences between both borderline and free (CHD_bord analyses) and affected and free (CHD_aff analyses) became obvious. Heritability estimate for CHD_bord was significantly different from zero, and additive genetic correlations between the BV univariately predicted for CHD_bord and CHD_aff were positive, but far from unity. Accordingly, dogs with CHD grade B should neither be considered healthy nor clearly affected with respect to CHD. CHD grades A and B should not be combined for genetic analyses to make maximum use of the available phenotype information.

Elbow joint classification according to the IEWG has been used in this study as in most previous studies on CED. However, when comparing CED across studies, it must be taken into account that CED classification may differ between countries even if it is uniformly based on the IEWG standard. In the USA and the Scandinavian countries, elbow joints are classified exclusively according to the extent of arthrosis present in the joint. Specific elbow joint diseases do not automatically lead to change of CED status as it is the case in other countries, including Germany, The Netherlands, France, Italy, Switzerland and Belgium. Here, it is not important whether or not FCP, UAP or OCD are accompanied by arthroses as secondary changes; the primary lesions alone will cause the dog to be classified as affected by CED. In this study, the proportion of GSD with mild to severe CED was only 9.3%, which is lower than the figures found in literature for this breed. This difference cannot be explained by classification differences, because the same classification protocol has revealed considerably higher proportions in other GSD populations or subpopulations (Coopman *et al.* 2008: 12% in Belgium; Janutta *et al.* 2006: 14.1% in Germany; Sturaro *et al.* 2005: 19.7% in Italy). Furthermore, exclusion of all cases of FCP, UAP and OCD (CED-ARTH) further reduced the affection rate to 6.3% in this study, which is approximately threefold lower than CED affection rates in countries in which dogs showing specific elbow joint diseases alone are not considered as affected by CED (Mäki *et al.* 2001: 18.8% in Finland). Although this difference of CED-ARTH prevalences may be somewhat overestimated because of the possible presence of secondary arthrotic changes in at least some of the dogs with specific elbow joint diseases, it is still remarkable. Increasing awareness of breeders and breeding organizations of the importance of CED has led to an increase in voluntary examinations and later to obligatory examinations for CED in breeding animals. Breeding measures may have already caused some favourable development of CED in the German population of GSD as it has been documented for other countries (Mäki *et al.* 2002).

Information on radiographic findings in the elbow joints, for which the term borderline has been introduced by the IEWG, is sparse. In many studies, this category of uncertain disease relevance is not mentioned at all or has not been analysed separately, both with the effect that borderline cases were analysed as unaffected by CED. In our study, we distinguished between dogs free of any abnormal radiographic findings in the elbow joints (CED-0) and dogs classified as borderline (CED-1), resulting in the use of a five-point scale instead of the common four-point scale. This distinction was justified by our results regarding the heritability of CED_bord and the correlations between the BV univariately predicted for CED_bord and CED_aff which indicated significant similarity, but no uniform genetic background of borderline CED and distinct CED. Therefore, we recommend that, analogous to CHD, dogs with borderline findings should not be considered as healthy with respect to CED. High heritabilities have been estimated for CED in the Rottweiler with no distinction between borderline and mild CED (Heine *et al.* 2009). However, the considerable breed differences in the prevalences of CED borderline findings (31.8% in the Rottweiler in Heine *et al.* 2009; 6.7% in the GSD in this study) may imply

that etiopathology and disease relevance could also vary between breeds. As long as clear across-breed disease relevance of borderline CED has not been scientifically proven, genetic analyses should benefit from separate consideration of borderline findings, resulting in the extension of the official four-point scale of the IEWG which was the basis of most previous studies. In addition, different pathogenesis of the specific elbow joint diseases FCP, UAP and OCD makes it unlikely that they are all influenced by the same genes (Janutta & Distl 2008; Temwichitr *et al.* 2010). Accordingly, separate recording in the course of radiographic examination for CED will probably facilitate untangling of the genetic background of CED and distinct primary lesions in the canine elbow joint.

Concerning the prevalences and phenotype distributions of both CHD and CED, it must be kept in mind that because of the lack of population-wide screening for these and other diseases, it is not possible to quantify the role of voluntary exclusion of severe cases from official statistics. It has been shown on the basis of simulated data that selective non-reporting of clear cases of CHD affection, which has been surmised previously (Hamann *et al.* 2003; Coopman *et al.* 2008), may strongly interfere with reliable genetic evaluation (Stock & Distl 2010). Concerning the comparison between genetic studies, differences in data collection must be considered, such as voluntary or obligatory examination and submission of examination results for all dogs or only potential breeding dogs. In addition, it must be taken into account that different categorization of traits directly affects the estimated variance components, possibly limiting comparability of results.

On the basis of the distinctive categorical scales, moderate heritabilities in the order of 0.2–0.3 have been estimated for CHD in the GSD (Mäki *et al.* 2002; Hamann *et al.* 2003). In our sample from the German GSD population, heritability was 0.25 for the categorical trait CHD and 0.19–0.27 for the binary traits CHD_bord and CHD_aff. Agreement with reported genetic parameter estimates was lower for CED than for CHD what may only partly explained by differences in trait definition. Heritability of CED was 0.15 in a population, in which borderline was considered as unaffected and CED classification was exclusively based on the extent of arthroses (Finland; Mäki *et al.* 2002). According to our results, both the joint analysis of findings of unequal genetic background (CED-0 and CED-1) and the exemption of primary lesions such as FCP may have lowered the estimates for genetic variance and heritability of CED.

There is no literature referring to the comparison between CED borderline, affected and unaffected, but clear evidence of the hereditary nature of FCP has been already provided for the Labrador retriever (Padgett *et al.* 1995; Ubbink *et al.* 2000). Our heritability estimate for the binary trait FCP of 0.57 supports the assumption of relevant genetic determination of this primary lesion in the elbow joint. Given the very rare occurrence of UAP and OCD in our data, available information on these primary lesions was considered insufficient for reliable genetic evaluation. Literature confirms the quantitative predominance of FCP among the specific elbow joint diseases which may lead to arthrotic changes in terms of CED (Janutta *et al.* 2008). Genetic studies with focus on the primary lesions in the elbow joint indicated independent inheritance or negative genetic correlations between them (Padgett *et al.* 1995; Janutta *et al.* 2006). However, different data sources may be needed to get a suitable basis for genetic correlation analyses of FCP, UAP and OCD.

Differences between current and previous results were also seen apart from those relating to varying trait definitions. A comparatively low heritability of 0.18 was estimated in the same population and with the same distinctive trait definition as it has been used in this study (Janutta *et al.* 2006). Changing practices of CED screening in the SV may have caused larger additive genetic variance among the dogs with available information on CED phenotype in this study when compared to the previous one. Examination for CED was voluntary for most of the 2645 GSD from birth years 1998 to 2002 that were considered in the study of Janutta *et al.* (2006), whereas it was mandatory for all of the 28 011 GSD from birth years 2001 to 2007 of this study that were intended to be used for breeding as of 2002. Obligatory elbow radiography for potential breeding animals has been introduced earlier in other breeds, for example the Rottweiler. Our heritability of 0.31 for the categorical trait CED is well in line with the estimates obtained in respective dog populations, for which heritabilities mostly ranged between 0.2 and 0.4 (Grøndalen & Lingaas 1991; Beuing *et al.* 2000; Mäki *et al.* 2002; Heine *et al.* 2009).

Because large-scale examination of canine elbow joints has only recently been introduced in several dog populations, there are a few genetic studies addressing the correlations between CHD and CED. Using data from obligatory CHD and voluntary CED

examinations, the additive genetic correlation between CHD and CED was estimated to be zero in the Finish GSD population (Mäki *et al.* 2002). On the basis of the SV data with CHD and CED information being required for breeding approval since 2002, we found moderately positive genetic correlations of 0.3 between the two dysplasias. This result was stable regardless of whether or not cases of visible primary lesion were included in the group of CED affected dogs. This means that a dog with high CHD disposition is more likely to be also disposed to develop CED than a dog with low CHD disposition. Genetic evaluation for CHD and CED will therefore benefit from a multivaraite approach. Furthermore, the negative additive genetic correlation estimate between FCP and CED-ARTH indicated at the same time that the genetic background of CED as it is currently defined according to the IEWG is not homogeneous. The primary lesions in the elbow joints should therefore be recorded in the course of examination for CED, because only specific breeding measures will assure maximum selection response. Given the relevant genetic determination of CHD, CED-ARTH and FCP, future breeding strategies to reduce the prevalences of CHD and CED may be based on BV. Because BV reflecting the genetic disposition for these diseases are expressed on continuous scales, they are much more suitable to distinguish between individuals than the disease phenotypes. According to the results of this study, highest selection efficiency will be achieved via multivariate genetic evaluation which accounts for the genetic correlations and therewith includes FCP as a separate trait.

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Supporting Information

Additional Supporting Information may be found in the online version of this article:

Figure S1 Joint distributions of relative breeding values (RBV) for the traits CHD_bord and CHD_aff in the 16,580 parents of informants.

Figure S2 Joint distributions of relative breeding values (RBV) for the traits CED_bord and CED_aff in the 16,580 parents of informants.

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