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Short communication

Prevalence and segregation analysis of dermoid sinus in Rhodesian Ridgebacks

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ABSTRACT

Rhodesian Ridgebacks are dogs with a characteristic dorsal hair ridge with backward-growing hair. Dermoid sinus was reported as a prevalent congenital condition in ridged dogs and as a sporadic finding in other dog breeds. This condition presents as a tubular skin indentation to variable degree into underlying tissues on the dorsal midline or cranial or caudal to the ridge. In the present study, data from 12,700 puppies born to 1622 litter from Rhodesian Ridgebacks in 2001–2019 in Germany were analysed for the prevalence of dermoid sinus and ridgless animals. Data from litters with dogs segregating for dermoid sinus were used to test compatibility with an autosomal recessive Mendelian trait. Overall prevalence of dermoid sinus in 12,700 puppies was 2.53%. In 1269 litter with only ridged animals, prevalence was 2.81%. In 46 litters, segregation of ridgeless dogs was observed, and two ridgeless animals had dermoid sinus. The overall trend for dermoid sinus prevalence significantly decreased by −0.099% per birth year, whereas a significant trend for ridgelessness was not found. A more complex genetic determination for dermoid sinus seems likely, due to the insufficient fit of a monogenic autosomal recessive model of inheritance and a heritability estimate of 0.78 ± 0.11. Genetic correlation with ridgelessness was −0.11. In conclusion, our data revealed a decreasing trend for the prevalence of dermoid sinus and a complex genetic basis for this condition. The ridge locus was unlikely to determine the expression of dermoid sinus, given the low segregation ratio for dermoid sinus in a population selected for the ridge allele.

A dorsal hair ridge with backward-growing hair is characteristic for Rhodesian and Thai Ridgebacks, and Vietnamese Phu Quoc dogs (Bell et al., 2012; Salmon Hillbertz and Andersson, 2006). Dogs from ridged breeds can have a dermoid sinus, a type of congenital malformation, and this developmental anomaly is sporadically seen in dogs of many other breeds (Lambrechts, 1996; Booth, 1998; Salmon Hillbertz et al., 2007; Kiviranta et al., 2011; Bell et al., 2012; Barrios et al., 2014). Dermoid sinus is caused by an incomplete separation of the ectoderm and neuroectoderm during early embryonic development. The result is a tubular skin indentation in the dorsal midline extending into subcutaneous tissue or up to the spinal dura mater. Six different types are recognised, depending on their extent into underlying tissues and opening to the skin surface (Mann and Stratton, 1966; Booth, 1998; Tshamala and Moens, 2000; Kiviranta et al., 2011). Typical locations in Rhodesian Ridgebacks are the areas in the front or the back of the ridge, the dorsal cervical, cranial thoracic, lumbosacral and coccygeal area (Hathcock et al., 1979; Fatone et al., 1995; Wagner et al., 2007). A nationwide health survey of the Rhodesian Ridgeback club of US (RRCUS) reported a prevalence of 5.3% for dermoid sinus in data from 1263 dogs (Miller and Tobias, 2003). Prevalence of dermoid sinus in Swedish Rhodesian Ridgebacks was 82/1040 (7.88%) (Salmon Hillbertz, 2005).

Different modes of inheritance have been proposed for dermoid sinus in Rhodesian Ridgebacks, including autosomal recessive, autosomal incomplete dominant, two recessive loci, or complex (Lord et al., 1957; Hofmeyr, 1963; Mann and Stratton, 1966; Salmon Hillbertz, 2005). A 133-kb duplication on dog chromosome 18 involving the genes *FGF3*, *FGF4*, *FGF19* and *LTO1* was identified as the ridge locus in Rhodesian and Thai Ridgebacks with a dominant allele determining the ridge (Salmon Hillbertz et al., 2007). Based on data from 42 Rhodesian and 12 Thai Ridgebacks with an association among the ridge genotypes and occurrence of dermoid sinus, a simple genetic model was proposed with ridgeless dogs as homozygous wildtype r/r, ridged dogs as r/R or R/R for the ridge allele and ridged dogs with dermoid sinus as homozygous mutant R/R. In contrast to the proposed genetic model, comparison of the observed with the expected segregation ratios of dermoid sinus in Swedish Rhodesian Ridgebacks was not conclusive for a recessive Mendelian trait (Salmon Hillbertz, 2005).

In the present study, an analysis was performed to study the

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prevalence of dermoid sinus and ridgelessness, the mode of inheritance of dermoid sinus and correlations among both conditions in Rhodesian Ridgebacks bred according to the rules of the Fédération Cynologique Internationale (FCI) in the DZRR (Deutsche Züchtergemeinschaft Rhodesian Ridgeback e.V.) in Germany. Records from 12,700 puppies registered in the years 2001–2019 were included. All Rhodesian Ridgeback puppies born alive recorded in the DZRR are inspected by breed wardens for breed relevant traits and visible abnormalities, particularly for dermoid sinus. Breed wardens are trained to diagnose dermoid sinus and register the ridge. According to DZRR breeding regulations, all dogs intended for breeding must be ridged and free from dermoid sinus. Analyses of variance were performed using a generalized linear model for the binary variate occurrence of dermoid sinus (see Appendix: Supplementary Tables S1–S2). Additionally, a bivariate generalized linear model was tested for both binary variates, dermoid sinus and ridgelessness, under the assumption of a logit-normal distribution (see Appendix: Supplementary Tables S3). A bivariate animal model was used to estimate heritabilities simultaneously for the presence of dermoid sinus and ridgelessness as binary traits using the software VCE (Groeneveld et al., 2008. VCE 6.0.2. Co-variance components estimation package, Institute of Farm Animal Genetics).

The animal model was as follows:

$$y_{ijk} = \mu + sex_i + b \times birth\ year_j + a_k + e_{ijk},$$

where y_{ijk} is the presence of a dermoid sinus or ridgelessness of the *ijk*-th dog, μ is a model constant, sex_i is a fixed effect, b a linear regression coefficient on birth year, a_k is the random additive genetic effect of the *k*-th dog (k = 1–12,700), and e_{ijk} is an unknown random residual effect.

Pedigree data included up to eight generations. In order to test familial segregation of dermoid sinus for Mendelian inheritance, the Singles method was used (Davie, 1979). Segregation analysis should determine whether the data collected are compatible with a recessive Mendelian trait. We compared the estimated segregation frequency expressed as a probability that an offspring is affected by dermoid sinus ($\hat{p}$) with the assumed probability (p_0) derived from the autosomal recessive Mendelian model of inheritance. For a monogenic autosomal recessive mode of inheritance and both parents in a set of full sib families being unaffected, the null hypothesis for the true value of p is $p_0 = 0.25$. Assuming incomplete penetrance (<1.0) for monogenic autosomal recessive models, the true value of p is $p_0 = 0.25$ x penetrance. For the most straightforward use of the Singles method under avoiding a biased estimate of the segregation ratio, all families with affected offspring are included in the data. The segregation frequency is estimated as:

$$\hat{p} = \frac{R - J}{T - J}$$

and its variance using

$$var\ (\hat{p}) \sim \frac{(R-J)(T-R)}{(T-J)^3} + \frac{2Q(T-R)^2}{(T-J)^4}$$

$$= var(\hat{p}) \sim \frac{(T-R)}{(T-J)^3}\left\{R - J + 2Q\frac{(T-R)}{(T-J)}\right\}$$

with R being the total number of affected offspring in the available data, T the total number of all examined offspring in the available data, J the total number of families with just one affected offspring, and Q the total number of families with two affected offspring. The null hypothesis is then tested using:

$$Z^2 = (\hat{p} - p_0)^2 / var(\hat{p}),$$

which is approximately distributed as χ^2 with one degree of freedom.

If the calculated Z^2 value is not significant at $P < 0.05$, the data are consistent with an autosomal recessive Mendelian mode of inheritance and expression of the trait when offspring are homozygous for the recessive allele in the one-locus model. We tested all families segregating for dermoid sinus and the subset of litters where all animals were ridged.

Assuming an epistasis model, only the homozygous recessive animals susceptible for dermoid sinus under an autosomal recessive Mendelian model can express dermoid sinus when they are homozygous rigded (R/R at the ridge locus). The probability of dermoid sinus equals p = dermoid sinus given the R/R genotype. The epistatic effect of the R/R genotype is accounted for by the penetrance. Penetrance is calculated from the expected R-allele frequency deduced from present data. Frequency of r/r animals equals 0.067 with corresponding r- and R-allele frequencies of 0.2588 and 0.7412 under the Hardy-Weinberg equilibrium. Expected genotypic distributions using these allele frequencies are 0.549 R/R, 0.384 R/r and 0.067 r/r. Under an epistasis model, the probability of expression of a dermoid sinus equals p (dermoid sinus | 0.549). This means that only among the expected 0.25 for dermoid sinus-susceptible offspring, the proportion of 0.549 R/R dogs are expected to develop a dermoid sinus. The remaining susceptible offspring will not have a dermoid sinus because they have not the R/R genotype at the ridge locus. The epistasis model reduces the expected segregation ratio of dermoid sinus for the true value of p to $p_0 = 0.1373$ (=0.25 × 0.549) in all segregating families. In families only with ridged offspring, expected frequency for R/R genotypes is 0.589 (=0.549/[1−0.067]), leading to an expected segregation ratio for dermoid sinus of $p_0 = 0.1473$ (0.25 × 0.589).

Unequal litter size may influence segregation ratios. A correction can be performed using the following formula:

$$q^* = q/(1 - p^s)$$

with q* corrected segregation ratio, q expected homozygous recessive genotypic frequency, p = 1-q and s = litter size (Nicholas, 1982). Using correction for litter size (9.6 in data sets employed) increases the expected segregation ratio under an autosomal recessive Mendelian model from 0.25 to 0.267.

In 1622 litters with 12,700 offspring, there were 321 (2.53%) animals with a dermoid sinus. Prevalence of dermoid sinus was 264/9409 (2.81%) when litters with only ridged animals were sampled and 57/3291 (1.73%) when litters with at least one ridgeless animal were analysed (Table 1). Ridgelessness was present in 851 (6.70%) animals. The number of litters segregating for both conditions, dermoid sinus and ridgelessness, was 46, including 455 offspring. Among these 46 litters, two ridgeless animals with dermoid sinus were observed. All parents in the present study were ridgedback and diagnosed negative for dermoid

Table 1
Segregation frequencies and contingency coefficients (CC) for dermoid sinus and dorsal ridge in litters segregating for dermoid sinus (DS+), dorsal ridge (RR+) or both conditions, dermoid sinus and dorsal ridge.

Number of animals/ litters	DS-/ RR+	DS-/ RR-	DS+/ RR+	DS+/ RR-	χ^2	*P*	CC[a]
Litters segregating for dermoid sinus[b]							
2370/246	1935	114	319	2	13.89	<.0001	0.079
Litters segregating for dermoid sinus using litters with all siblings ridged[c]							
1915/200	1651	0	264	0	–	–	–
Litters with all siblings ridged							
9409/1269	9145	0	264	0	–	–	–
Litters with at least one ridgeless sibling							
3291/353	2385	849	55	2	14.73	<.0001	0.067
Litters segregating for both conditions							
455/46	284	114	55	2	14.45	<.0001	0.175

DS-, unaffected by dermoid sinus; DS+, affected by dermoid sinus; RR+, ridgedback; RR-, ridgeless.
[a] CC is calculated as $\sqrt{\chi 2/(\chi 2 + n)}$; *n* = sample size (Sachs, 1978).
[b] Litters with at least one DS + animal.
[c] Litters with at least one DS + animal and only ridged siblings.

sinus. Testing the joint distribution of dermoid sinus and ridgelessness for equal marginal frequencies produced a significant deviation from their expected values ($\chi^2 = 19.45$; $P < 0.0001$) in all litters and litters segregating for both conditions ($\chi^2 = 14.45$; $P < 0.0001$). Prevalence of dermoid sinus significantly decreased by -0.099% per birth year, whereas a significant effect of birth year for ridgelessness was not evident. Using a bivariate generalized linear model with dog as a random effect produced a correlation of −0.042 among dermoid sinus and ridgelessness. The heritability estimates (h^2) with their standard errors with a bivariate animal model were 0.78 ± 0.11 and 0.94 ± 0.09 for dermoid sinus and ridgelessness, after transformation to the underlying scale (Dempster and Lerner, 1950). The phenotypic and genetic correlations of dermoid sinus with ridgelessness were −0.04 and −0.11 ± 0.071, respectively. Efficiency of the indirect selection response (R_{ind}), when using ridgelessness as breeding trait can be derived as follows:

$$R_{ind} = (\text{h for ridgelessness} \times r_g)/h$$

for dermoid sinus (Falconer, 1981). Selection on ridgelessness instead of dermoid sinus would only reach a relative efficiency of 12.1% in comparison to direct selection on dermoid sinus.

The tests on an autosomal recessive mode of inheritance employing the Singles method for occurrence of dermoid sinus were significantly different from the null hypothesis $p_0 = 0.25$ for the true value of p ($P < 0.0001$), and thus, rejected the hypothesis of a recessive Mendelian trait for dermoid sinus (see Appendix: Supplementary Table S4). Even in an epistasis model allowing only homozygous riged animals (R/R) to express dermoid sinus, the null hypothesis $p_0 = 0.1373$ had to be rejected. In a previous report from Sweden, a small percentage (5–10%) underreported dogs with dermoid sinus was assumed (Salmon Hillbertz, 2005). When taking into account this assumption from the Swedish study, the outcome of the segregation analysis was not affected. Assuming a two-locus model with two independent autosomal recessive loci and only double homozygous recessive genotypes as affected, the null hypothesis results in $p_0 = 0.0625$ (=0.25 × 0.25). This null hypothesis is equivalent to a one-locus model after imposing a penetrance of 0.25. In this case, the observed frequency fits with p_0. It is very unlikely that a penetrance estimate of 0.25 has been caused through underreporting (Salmon Hillbertz, 2005), especially when there is regular recording of all puppies born alive, such as in the DZRR.

The high heritability estimate supported a genetic basis for dermoid sinus in Rhodesian Ridgebacks, but segregation analysis ruled out a monogenic inheritance. A more complex genetic basis for dermoid sinus seems very likely. Segregation ratios indicated that at least two independent recessive loci may be involved. Since the genetic correlation between dermoid sinus and ridgelessness is not far from zero, this supports the assumption that both conditions are different genetic traits. Estimated frequency of the r-allele in progeny is 0.259, resulting in expected 54.9% R/R progeny presumably affected by dermoid sinus using the model of Salmon Hillbertz et al. (2007). This estimate is far from the observed frequency of dermoid sinus in our data and a previous report (Salmon Hillbertz, 2005).

Our data analysis provided no evidence that dermoid sinus is a Mendelian trait, or that a model assuming the ridge locus is responsible for both conditions in the expression of the ridge and dermoid sinus. We found evidence of a complex genetic basis for dermoid sinus. Increasing selection pressure on ridgelessness might not lead to a substantially higher correlated selection response to reduce dermoid sinus prevalence, because of an estimated genetic correlation close to zero.

Conflict of interest

None of the authors of this paper have a financial or personal relationship with other people or organizations that could inappropriately influence or bias the content of the paper.

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Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:https://doi.org/10.1016/j.tvjl.2022.105803.

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