

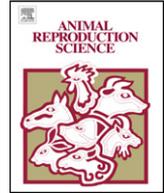


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Animal Reproduction Science

journal homepage: www.elsevier.com/locate/anireprosci



Relationship of cryptorchidism with sex ratios and litter sizes in 12 dog breeds

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ARTICLE INFO

Article history:

Received 20 February 2008

Received in revised form 23 May 2008

Accepted 1 July 2008

Available online 8 July 2008

Keywords:

Dogs

Cryptorchidism

Sex ratio

Litter size

ABSTRACT

The aim of this study was to identify the influence of genetic carrier-ship for cryptorchidism on litter sizes and sex ratios in the offspring. Weaning data of 11,230 litters in 12 purebred dog breeds were evaluated. Parents were classified as cryptorchidism 'carriers' (C) when at least one of their offspring was found cryptorchid. Subsequently the effects of 'carrier' and 'non-carrier' (NC) parents on their litters were studied.

In litters from C × C parents we found an increased number of males per litter in all breeds, a reduced number of females per litter in 8 breeds and an increased litter size in 11 breeds in comparison with litters from NC × NC parents. Over all breeds the effects on litter size, on number of males per litter and on sex ratio were highly significant. Mixed litters from C × NC and NC × C did not show these effects and were not significantly different from the NC × NC offspring.

Our results suggest a general mechanism in the dog species which causes cryptorchidism as well as increased male/female ratios and increased litter sizes. A consequence of such a mechanism is that selection in favor of increasing reproduction output frustrates selective efforts to eliminate cryptorchidism.

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1. Introduction

Cryptorchidism is the failure of the testes (one or both) to descend into the scrotum through the inguinal canal. Cryptorchidism in dogs may have undesirable effects such as infertility, a higher risk for tumor formation and feminization (Reif and Brodey, 1969; Post and Kilborn, 1987; Nieto et al., 1989). Bilateral cryptorchids are sterile; dogs with one descended and one retained testis are fertile. The condition occurs in other mammalian species as well (Amann and Veeramachaneni, 2007).

Prevalences of cryptorchidism in domestic animals have a wide range depending on species and breed (Amann and Veeramachaneni, 2007). In comparison to the human situation the genetic components of cryptorchidism in domestic animals still remain unclear. In animal breeding the occurrence of cryptorchidism leads to an economic loss and a decreased selection potential of male breeding stock. Breeding organizations are well aware of this problem but as long as the genetic background is not clear no great effort is made to eliminate the disorder.

Descriptions of cryptorchidism go back as far as the 16th century (Amann and Veeramachaneni, 2007). There is general agreement that in most cases cryptorchidism is caused by a genetic defect. Theories about cryptorchidism in dogs date back to a report by Härtl (1938) on a sample of 57 litters of German Boxers, in which 23% of 168 males were cryptorchids. Based on these data Härtl supposed a simple autosomal sex-limited recessive trait.

In 1964 Brandsch found that litters with cryptorchids had an abnormally high sex ratio in favor of males. He supposed that this might be due to a lethal effect for females by the gene(s) causing cryptorchidism. In German Shepherds he found 125 males per 100 females in litters containing cryptorchids compared to an overall sex ratio of 102. Using Härtl's Boxer data he calculated ratios of 156 and 102, respectively.

Sittmann (1976) re-analyzed the data of Härtl and Brandsch and his conclusions negate Brandsch's suppositions regarding a high sex ratio (in favor of males) and lethal effects on females related to cryptorchidism. He proved an extensive under-reporting on cryptorchid males in Brandsch's data and argued that the probability of detecting affected males was higher in large litters with a high sex ratio. In his study, based on maximum likelihood estimates in full-sib and paternal half-sib families, the viability of affected males and of females with the cryptorchid genotype was normal and the latter seemed to be able to reproduce. He concluded that cryptorchidism in the German Boxer was caused by a simple autosomal recessive gene but did not exclude the possibility of a polygenic model with threshold points. Sittmann considered the severity of the disorder (unilateral versus bilateral) to be subject to environmental factors and/or modifier genes.

The present state of knowledge suggests that cryptorchidism is caused by the interaction of genetic, epigenetic and environmental factors (Amann and Veeramachaneni, 2006). Although a whole range of genes has been implicated in the regulation of testicular descent in humans (Ivell and Hartung, 2003; Klönisch et al., 2004; Yoshida et al., 2005) no single gene is mutated in more than 10% of cryptorchids (Amann and Veeramachaneni, 2007).

Since only limited effort has been put in larger scale studies on cryptorchidism in dogs it is not surprising that there is no clarity about the genetic basis of cryptorchidism. The role of environmental factors affecting testicular descent is not yet clear as only few studies are available (Thonneau et al., 2003).

In order to better underpin the reproduction biology of the disorder we have evaluated and compared large-scale structural reproduction data in 12 dog breeds in the Netherlands. Our main goal was to evaluate in detail the associations of cryptorchidism with male/female ratio (sex ratio) and with litter size over a large spectrum of dog breeds.

2. Materials and methods

The data on cryptorchid dogs in this study were derived from extensive health inventories in the period 1994–2006 (Gubbels et al., unpublished data). Twelve breeds were included in this study: Beagle, Border Terrier, German Boxer, Cairn Terrier, Chow Chow, Drentse Partridge Dog, German Hound, Flatcoated Retriever, Schapendoes, Scottish Sheepdog, Shetland Sheepdog and West Highland White Terrier.

The weaning data were analyzed per breed and over all these breeds. The breed populations were defined as 'all animals belonging to the breed and registered in the Dutch studbook for pedigree dogs (NHSB)'. The NHSB is an all-breed studbook that registers all pups between 6 and 8 weeks of age. The breeder is obliged to register all pups to be weaned. The NHSB does not register the number of animals born. Therefore the mating results in this study were expressed as number of males and females weaned.

Per breed the period included in the analysis was determined by the availability of information on affected animals. All cryptorchid males in this study were identified at an age of 12 months or older. The litter data on the affected litters and all their contemporaries were extracted from the studbook. In the analysis the data of 11,230 litters comprising 26,547 males and 26,246 females were evaluated.

Parents of at least one identified cryptorchid were marked as (known) 'carriers' (C). All other parents were marked as 'non-carriers' (NC). For each of the breeds involved the group of litters from two carrier parents and the population average were compared with respect to litter size and with respect to number of males and females per litter. In order to avoid the bias that results from the analysis of affected litters only, the entire progeny groups of carrier sires and dams were included in the analyses. Differences over all 12 breeds were tested in a Sign Test (Abdi, 2007) on breed level which is a binomial test of the deviation from an expected 50:50 ratio for positive and negative signs when there is no systematic difference between two groups. Exact binomial probabilities were evaluated using the binomial test procedure in the software package 'R' (R Development Core Team, 2005).

To describe the population characteristics for each breed as well as for the total group the sex ratio, the incidence of cryptorchidism in males and the percentage of cryptorchids in litters from two carriers were calculated. The average litter sizes and the sex ratios were compared for the four possible parental combinations between carriers and non-carriers. The litters from two non-carrier parents were used as control group.

The differences in the four mating combinations were evaluated in a joint analysis of all data with a linear model that included breed effects (12 levels) and the four mating types as a four-level factor. The linear model was fitted using the *lm* procedure in the statistical software package 'R' (R Development Core Team, 2005), and the summary procedure was used to obtain the standard errors and the *t*-test to test for differences between the C × C, C × NC and NC × C mating types with the NC × NC mating type.

Tests for significant differences were applied on number of males per litter, on litter size and on the numerical imbalance between the sexes in a litter. For the latter criterion the number of males minus the number of females was used as an indicator for the sex ratio. Significance was considered when $P < 0.05$.

3. Results

Table 1 gives an overview of the sex imbalance at weaning in the populations included in this study and in the litters from C × C parents within each population. In the whole data set there were 4 breeds with more females than males weaned and 8 breeds with less females than males weaned, but the differences were not significant (Sign Test, $P = 0.388$). The overall sex ratio calculated as the average of the 12 breeds in this study was 101.6 males per 100 females. However, when looking at the reproduction data from C × C parents it appeared that all 12 breeds had a higher number of males than females. The overrepresentation of males was highly significant ($P < 0.001$). The overall sex ratio in litters from C × C parents calculated as the average of the 12 breeds was 135.7 males per 100 females. The percentages of cryptorchid males in the populations are indicative for the mating combinations applied in recent generations. The percentages of cryptorchids in C × C litters give an indication of the possible genetic basis for cryptorchidism.

The comparison of reproduction results of the four parental combinations given in Table 2 showed that litters of C × C parents differed highly significantly from NC × NC litters with regard to number of males per litter (P -value = 2×10^{-16}) and litter size (P -value = 5×10^{-6}). A far weaker significance was found for the number of females (P -value = 0.042). The overall effect on females was that litters of C × C parents had slightly less females than NC × NC litters. Mixed litters of C × NC or NC × C parents did not differ from NC × NC litters. Hence, effects were only seen in litters where both parents were carriers for cryptorchidism and not in litters where only one parent was a carrier. In the joint analysis of data

Table 1

Overview of the most relevant reproduction characteristics at weaning of the populations included in this study, 'sex ratio' is defined as the number of males per 100 females

	Reproduction data of all litters analyzed						Reproduction data of matings between carriers				
	# of litters	# of males	# of females	Sex ratio	# of crypt. males	% crypt. in the population	# of litters	# of males	# of females	Sex ratio	% crypt. in C × C
Beagle	244	644	578	111.4	12	1.9	14	43	25	172.0	27.9
Border Terrier	249	558	559	99.8	26	4.7	34	103	68	151.5	25.2
German Boxer	398	1,018	991	102.7	37	3.6	33	119	84	141.7	31.1
Cairn Terrier	1,407	2,828	2,765	102.3	19	0.7	25	63	43	146.5	30.2
Chow Chow	207	416	432	96.3	11	2.6	13	38	22	172.7	28.9
Drentse Partridge Dog	1,224	3,779	3,542	106.7	76	2.0	116	419	315	133.0	18.1
German Hound	96	223	221	100.9	8	3.6	16	46	37	124.3	17.4
Flatcoated Retriever	438	1,692	1,644	102.9	10	0.6	12	52	50	104.0	19.2
Schapendoes	1,068	3,222	3,282	98.2	18	0.6	22	85	71	119.7	21.2
Scottish Sheepdog	1,920	5,118	4,837	105.8	49	1.0	78	256	192	133.3	19.1
Shetland Sheepdog	1,914	3,316	3,293	100.7	106	3.2	177	354	280	126.4	29.9
West Highland White Terrier	2,065	3,733	4,102	91.0	33	0.9	79	156	152	102.6	21.2
Total	11,230	26,547	26,246		405		619	1734	1339		
Averages	936	2,212	2,187	101.6	34	2.1	52	145	112	135.7	24.1

Table 2

Comparison of reproduction data at weaning in four mating combinations between cryptorchidism 'carrier' (C) parents and 'non-carrier' (NC) parents with the *P* values for significant differences compared to the respective trait in the NC × NC group, obtained from a joint analysis of all data

	Matings between C sire and C dam			Matings between C sire and NC dam			Matings between NC sire and C dam			Matings between NC sire and NC dam		
	# of males per litter	# of females per litter	litter size	# of males per litter	# of females per litter	litter size	# of males per litter	# of females per litter	litter size	# of males per litter	# of females per litter	litter size
Beagle	3.07	1.79	4.86	2.63	2.65	5.28	1.75	2.25	4.00	2.63	2.32	4.95
Border Terrier	3.03	2.00	5.03	1.96	2.46	4.42	1.44	2.89	4.33	2.29	2.10	4.39
German Boxer	3.61	2.55	6.15	2.45	2.61	5.06	1.00	1.50	2.50	2.49	2.41	4.90
Cairn Terrier	2.52	1.72	4.24	1.95	1.99	3.94	1.82	1.95	3.77	2.01	1.97	3.98
Chow Chow	2.92	1.69	4.62	1.97	2.24	4.21	2.00	1.00	3.00	1.94	2.13	4.07
Drentse Partridge Dog	3.61	2.72	6.33	3.02	2.79	5.82	2.86	3.15	6.02	3.05	2.94	5.99
German Hound	2.88	2.31	5.19	2.09	3.18	5.27	2.50	1.50	4.00	2.22	2.18	4.40
Flatcoated Retriever	4.33	4.17	8.50	3.61	4.15	7.76	3.33	2.33	5.67	3.89	3.68	7.58
Schapendoes	3.86	3.23	7.09	3.16	2.73	5.90	2.70	2.65	5.35	2.99	3.11	6.10
Scottish Sheepdog	3.28	2.46	5.74	2.74	2.51	5.26	3.19	2.19	5.38	2.59	2.53	5.11
Shetland Sheepdog	2.00	1.58	3.58	1.74	1.69	3.43	1.66	1.75	3.41	1.69	1.76	3.45
West Highland White Terrier	1.97	1.92	3.90	1.81	1.98	3.79	1.26	1.58	2.84	1.80	2.00	3.80
Averages	3.09	2.34	5.44	2.43	2.58	5.01	2.13	2.06	4.19	2.47	2.43	4.89
<i>P</i> values	2×10^{-16}	0.042	5×10^{-6}	0.477	0.860	0.693	0.100	0.536	0.096	–	–	–

presented in Table 2, the four parental mating combinations accounted for only a small portion (<1%) of the explained variance.

Male excess (number of males minus number of females per litter) in litters from C × C parents proved to differ highly significantly (P -value = 2×10^{-12}) from the comparable result from NC × NC parents (Table 3). Again, mixed litters from C × NC or NC × C parents did not differ significantly from NC × NC litters, and hence effects were only seen in litters where both parents are cryptorchidism carriers (C × C).

4. Discussion

In the analyses presented here we included all available data, i.e. also the data of breed populations that did not (seem to) correspond completely to the general trends observed in most populations. Despite the inclusion of these populations we could prove highly significant global effects of carriership for cryptorchidism on reproductive performance at weaning level.

Exclusion of the 'not completely corresponding populations' would have introduced a bias towards confirming the hypotheses that were subject of this study. Therefore we have included all available data. If the effects were not consistent among populations, the joint analyses would have failed to produce significant results.

The Dutch studbook for pedigree dogs, the NHSB, only registers weaning data, so birth data and pre-weaning losses were not available for our study. Therefore the bare conclusions of this study pertain to effects of 'fertility at weaning'. Fertility at weaning is an important characteristic in evolutionary biology (as in artificial breeding and selection programs) because it is most closely related to 'fitness', i.e. to the number of an animal's reproducing progeny and, as a consequence, to the spread of its genes in the population. Fact is that C × C litters ended up at weaning age with highly significant increased numbers of pups per litter, increased numbers of males per litter and increased sex ratios.

Litter size and sex ratio at birth, as at weaning, are first of all breed-dependent, they are secondly dependent on the level of inbreeding within the subpopulation of the breed. The reproductive performance of each individual is determined by its genotype and by its past and actual interactions with its environment. When analyzing the reproductive performance of females, the genotype of the offspring is part of the environment of the dam.

Cryptorchidism is a disorder that influences the development of affected individuals from an early embryological stage on, so it may have physiological and numerical consequences at all levels of the reproductive process. It even might influence conception rates. Further detailed studies are needed to evaluate the effects of cryptorchidism on the pre-weaning part of life.

The increases were most probably due to extra pups born, but an additional effect may have arisen from an altered balance in the death rate between sexes before weaning.

Cryptorchidism is a disorder with a variable phenotypic expression: unilateral versus bilateral, and variability in the location of the retained testicle(s). Some authors (e.g. Amann and Veeramachaneni, 2007) focused on the detailed differences in the phenotypic expression of cryptorchidism and considered the disorder as the common phenotypic end result of a multiplicity of different genetic and non-genetic disorders.

In our analyses we considered cryptorchidism as just one disorder. We neglected the differences in phenotypic expression assuming that they are caused by environmental factors and/or modifier genes. Indeed, in the offspring of two carrier parents all variants of cryptorchidism seem to have comparable consequences which supports the hypothesis of just one common genetic disorder with (a multiplicity of) modifying genes and/or environmental factors determining the variation in phenotypic expression.

The period included in this analysis for each of the breeds was determined by the availability of information on affected animals. Since it was impossible to identify all affected animals born in any given period of time with complete certainty, the group of non-carriers could include a (limited) number of parents that were 'hidden' carriers. Therefore, the calculated incidences and the calculated frequencies of cryptorchids in litters from two carrier parents should be interpreted as minimum values (Table 1).

In our study strikingly high sex ratios were found in litters containing cryptorchids. Brandsch (1964) also reported this phenomenon. Sittmann (1976) evaluated Brandsch's data; he suggested that the high

Table 3

Comparison of sex ratio and male excess at weaning in four mating combinations between cryptorchidism 'carrier' (C) parents and 'non-carrier' (NC) parents with the *P* values for significant differences compared to the respective trait in the NC × NC group, obtained from a joint analysis of all data

	Matings between C sire and C dam		Matings between C sire and NC dam		Matings between NC sire and C dam		Matings between NC sire and NC dam	
	Sex ratio	Male excess	Sex ratio	Male excess	Sex ratio	Male excess	Sex ratio	Male excess
Beagle	172.0	1.29	99.4	−0.02	77.8	−0.50	113.2	0.31
Border Terrier	151.5	1.03	79.5	−0.51	50.0	−1.44	108.9	0.19
German Boxer	141.7	1.06	93.8	−0.16	66.7	−0.50	103.0	0.07
Cairn Terrier	146.5	0.80	97.7	−0.05	93.0	−0.14	102.2	0.04
Chow Chow	172.7	1.23	87.8	−0.27	200.0	1.00	91.2	−0.19
Drentse Partridge Dog	133.0	0.90	108.1	0.23	90.9	−0.29	103.9	0.11
German Hound	124.3	0.56	65.7	−1.09	166.7	1.00	102.1	0.04
Flatcoated Retriever	104.0	0.17	87.2	−0.53	142.9	1.00	105.7	0.21
Schapendoes	119.7	0.64	115.7	0.43	101.9	0.05	96.3	−0.12
Scottish Sheepdog	133.3	0.82	109.0	0.23	145.7	1.00	102.2	0.06
Shetland Sheepdog	126.4	0.42	102.7	0.05	94.5	−0.10	95.8	−0.07
West Highland White Terrier	102.6	0.05	91.5	−0.17	80.0	−0.32	90.3	−0.19
Averages	135.7	0.75	94.8	−0.16	109.2	0.06	101.2	0.04
<i>P</i> values		2×10^{-12}		0.544		0.482		–

Only the trait male excess was subjected to statistical analysis, 'sex ratio' is defined as the number of males per 100 females, 'male excess' is defined as the number of males minus the number of females.

sex ratios could be an artifact caused by extensive under-reporting of cryptorchids combined with the higher probability of finding cryptorchids in larger litters and in litters with more males. In our set-up we avoided these effects by including the complete progeny groups of carrier parents, not just the affected litters.

We found that the sex ratios (males per 100 females) in litters from two carrier parents differed highly significantly from those in litters between two non-carrier parents (Table 3).

Brandsch (1964) supposed that the high sex ratios in litters with affected males resulted from lethal consequences of cryptorchidism on affected females. Our results of an increased litter size resulting from an increased number of males per litter and (on average) a slightly reduced number of females per litter (Table 2) do not support the idea of a lethal effect on females.

In our data there was only a just-significant reduction of females in litters from two carrier parents. In some of the breeds we even found an increased number of females in such litters. The reduction of females in $C \times C$ litters does not seem to be directly caused by cryptorchidism. Our results confirm Sittmann's conclusion (1976) that the viability of females with the cryptorchid genotype is fully normal. It is most likely that the decrease of females per litter in 8 out of the present 12 breeds was caused by increased competition in the uterus ('crowding') or during the pre-weaning period due to the increased number of males.

The increased number of females per litter in 4 out of 12 breeds (German Boxer, German Hound, Flat-coated Retriever and Schapendoes) even suggests a positive effect of the genetic basis of cryptorchidism on the number of weaned females per litter. The results may be explained by the assumption that the combination of two carrier parents resulted in an increase in number of males as well as a smaller increase in number of females per litter. The final result could then be determined by the limitations set by the average uterine capacity of the breed. Unfortunately in our study we had no means of determining the average uterine capacity per breed.

Uterine capacity is a characteristic of the dam (genotype, age, individual environmental factors). The level of utilization of that capacity is determined by the genotype of the embryos and/or their interaction with the maternal environment. It is unlikely that the increased reproductive success of $C \times C$ combinations was caused by increased fertility of the sperm of carrier males since we could not prove any effect in $C \times NC$ combinations. It is also highly unlikely that it was an effect of improved fertility (more eggs) of carrier dams; we did not find any effect in the combination with non-carrier males ($NC \times C$). Thus, it must have been an effect of increased fitness of the embryos from two carrier parents and/or their interaction with the maternal environment.

Cryptorchidism is a disorder with a negative economic impact in dog breeding. Cryptorchids are excluded from breeding and from dog shows by the regulations of the Federation Cynologique International. With respect to health, undescended testicles may need surgical removal in order to avoid the development of tumorous testicular tissue. Most breeders tend to select against the disorder. The increased reproductive success of litters between two carrier parents (Table 2) indicates a selective advantage related to cryptorchidism.

The litter sizes in parental combinations of a carrier and a non-carrier did not differ significantly from those of the control group, nor did the number of males per litter or the sex ratio. We conclude that the selective advantage is not a characteristic of either the carrier sire or the carrier dam but instead is a characteristic of the combination of two carrier parents; in other words, it is a characteristic of the pups from two carrier parents. This is probably an important part of the answer to the question why cryptorchidism persists on relatively high levels in dog populations in spite of a permanent selection pressure against it by exclusion of affected males and, in some breeds, even of identified carrier parents.

In farm animals the negative economic impact of cryptorchidism is even larger. Dolf and co-workers (personal communication) confirmed our result in pigs, in which cryptorchidism also lead to a selective advantage and matings between carriers resulted in increased litter sizes. The relationship between cryptorchidism and reproductive success could be a more general process in mammalian species. An important aspect of the persistence of cryptorchidism could be that selection in favor of reproductive performance provokes an indirect selection in favor of cryptorchidism.

The frequencies of cryptorchids in litters from two carrier parents did not indicate different genetic disorders causing the phenotypic expression of cryptorchidism in the breeds studied (Table 1).

The overall frequency of 24.1% of affected males found in litters from two carrier parents may be compatible with a simple autosomal recessive inheritance of cryptorchidism, with effects of modifying genes and/or environmental factors that determine the exact phenotypic expression of cryptorchidism in affected animals. This conclusion is supported by the fact that in mating combinations with only one carrier parent none of the reproduction characteristics was found to differ significantly from those of the control group. If there were more loci involved and the phenotypic expression of cryptorchidism followed a threshold model, an intermediate effect would be expected in the reproductive performance of litters with only one carrier parent, but this was not found.

Our findings of the same effect of cryptorchidism-status of parents on reproduction in a wide range of breeds imply that the effect is likely based on a common mechanism. This implies that further study of this 'cryptorchidism effect' could reveal a fundamental biological mechanism affecting reproduction or vitality. With the same phenomenon appearing in many breeds, and probably in different species, genetic studies for mapping a causative gene would get a powerful impulse.

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