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Article *in* Journal of Heredity · September 1985

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The Journal of Heredity 76:393–394. 1985.

Heritable syndrome of skeletal defects in a family of Australian shepherd dogs

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ABSTRACT: A syndrome of multiple defects including cleft palate, polydactyly, and often syndactyly, shortened tibia-fibula, brachygnathism and scoliosis lethal to males is described in a family of Australian shepherd dogs. Female pups lack the cleft palate and survive, but may exhibit the other defects to a lesser degree than do males. Litter data suggest that the trait is inherited as an X-linked lethal gene, but the possibility of a sex-influenced autosomal allele cannot be ruled out. The syndrome may have arisen in conjunction with instability of the merle locus.

AN AUSTRALIAN shepherd bitch homozygous for the autosomal, incompletely dominant merle coat-color pattern gene was used in breeding trials to verify the occurrence of stable merle revertants. She had heterozygous merle parents and the extensively white coat, defective blue eyes, and deafness typical of a homozygous merle. It has previously been reported that she produced 66 pups by non-merle mates[5]. In the course of this breeding project an unusually large number of pups was observed with a syndrome of skeletal defects that usually included polydactyly in females and cleft palate with polydactyly in males. The syndrome was lethal to affected males. These defects were not observed in other pups born in this kennel from relatives of the bitch or sires of the pups.

Although cleft palate and polydactyly previously have been reported in dogs[1–4], possibly as genetic traits, they have not been described as traits of a single inherited syndrome. This report documents the occurrence of a syndrome of lethal skeletal defects, usually including cleft palate and polydactyly, in a family of Australian shepherd dogs that were all descendants of a single homozygous merle bitch.

Materials and Methods

The breeding data consisted of records for 32 litters produced by the original bitch, two unaffected daughters producing affected pups, four affected daughters and two affected granddaughters, for a total of 219 pups, at least 74 of which were affected. Twenty-two of these pups were produced by the original bitch (two litters) and an affected daughter (one litter) after the dams had been fed a vitamin-mineral supplement (Centrum, Lederle) during pregnancy. The data from the supplemented litters are considered separately from the other data. With the exception of the supplementation for three litters, the husbandry was the same for all bitches and litters as well as for unrelated bitches producing normal litters at the same kennel. All litters were purebred except two litters, one from the original bitch and one from an unaffected daughter, which were sired by Beagle dogs and are crossbred rather than purebred.

Results

The abnormalities in male pups consisted of cleft palate, syndactyly, polydactyly, shortened tibia-fibula, brachygnathism, and often scoliosis. None survived more than a few days. The cleft palates extended from the nasal planum in a few cases, or from the incisor area, to the caudal-most portion of the soft palate. The polydactyly usually consisted of extra digits in the foot proper, as distinct from lateral or medial dewclaws that are more proximally located, functionless digits. Other males were phenotypically normal and survived.

Affected females survived, and lacked the cleft palate and severe skeletal defects of the males. The various defects noted in females included polydactyly or syndactyly, an irregular pattern of palate ridges, irregular nasal planum, and occasionally extra teeth, a patchy glandular pattern on the tongue surface, and shortened tibia-fibula. Brachygnathism and scoliosis were not seen in affected females. In general, the defects in the females were mild and an affected phenotype could be difficult to recognize in the absence of progeny data.

The original bitch had no obvious skeletal abnormalities. She produced litters by both non-merle and merle sires, for a total of 68 pups in eight nonsupplemented litters (21 males and 47 females), of which 7 males and 14 females were affected. The affected pups were by her sire or by four males not closely related to her including one beagle dog. The crossbred litter consisted of two normal females. Of the two revertant non-merle pups she produced, one was an affected female, the other was an unaffected male.

Six daughters and two granddaughters of the bitch produced affected pups by 10 different males (including one beagle dog) for 21 litters. These litters included 55 male and 74 female pups, of which 22 males and 18 females were affected. The crossbred litter consisted of three normal males, one affected male, and five female pups. Other daughters in this family reproduced as well, but records of those that never produced an affected pup were not available. No surviving male used for breeding has sired affected pups, although a few of these have been used extensively in other kennels.

The litter data from the original bitch and her descendants that produced affected pups are summarized in Table I. The litters were classified by dam, and by whether or not the

Table I. Number of affected (A) and unaffected (U) pups produced by various classifications of dams for the skeletal lethal trait

	Pups							Litters			χ^2 values	
	male			female			Pups				male	
	A	U	total	A	U	total	total	N	avg. size	range	A:U	male:female
Original	7	14	21	14	33	47	68	8	8.5	2–13	2.33	9.94*
Unaff dams #3	3	8	11	1	16	17	28	4	7	2–10		
#4	2	4	6	1	8	9	15	2	7.5	7–8		
	5	12	17	2	24	26	43	14	7.25		2.88	1.88
Aff dams #2	4	6	10	4	7	11	21	4	5.25	3–8		
#5	1	2	3	2	3	5	8	1	8	—		
#6	2	3	5	5	4	9	14	3	4.67	1–7		
#7	5	1	6	1	12	13	19	3	6.33	5–8		
#8	3	6	9	2	5	7	16	3	5.33	3–8		
#9	2	3	5	2	1	3	8	1	8	—		
	17	21	38	16	32	48	86	15	6.26		0.42	1.16
Grand total (unsuppl.)	29	47	76	32	89	121	197	29	6.79		4.26*	10.23**
Supplemented litters	7	6	13	6	3	9	22	3	7.33	5–11	0.08	0.72
Grand total	36	53	89	38	92	130	219	32	6.84		3.25	7.68**

* $P < 0.05$; ** $P < 0.01$; all other values not significant

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dam was obviously affected with the syndrome. The litters supplemented during gestation are grouped separately at the bottom of the table. Percentages of affected pups of each sex are listed for the original dam, for the combined litters of the two unaffected dams, and the combined litters of the six affected dams. Significance of chi-square values calculated assuming 1:1 segregation ratios for male versus female and affected versus normal males are shown.

All of the bitches for which data are presented produced normal as well as abnormal pups when bred to either related or outcrossed males. Fewer than half of the male pups were affected for all classes of litters except the supplemented one, but the numbers were not significantly different by chi square test from an assumption of half the males being affected. Many fewer than half of the female pups were affected for all classes of litters. This is most likely due to the difficulty of detecting minimally affected females. Supplemented litters appeared to have a higher ratio than other litters of affected to unaffected pups of both sexes, but the numbers for this data set are small.

Discussion

Since no other lines in the kennel produced pups with this series of defects it is unlikely that the syndrome is due to an environmental condition and it is likely that it is an inherited trait. Affected pups were produced in crosses with unrelated (including crossbred) as well as with related sires so it is unlikely the inheritance is recessive. Affected daughters transmitted the defects to their sons and daughters, which is characteristic of a dominant allele. Some unaffected daughters produced the defect when bred to males unrelated to them, so the allele cannot be a completely penetrant dominant.

The data fit best either a sex-influenced autosomal dominant allele, or an X-linked allele that is lethal in the hemizygous condition and variably expressed or incompletely penetrant in heterozygous females. Among male offspring of females that produce affected pups, half are defective and die, half are normal and do not sire affected pups. Among female offspring of females that produce affected pups, some females are affected and produce affected pups; others are unaffected and do or do not produce affected pups. Apparently, the affected females are producing two classes of daughters, those with the male lethal that may or may not show partial expression in the carriers, and those without the lethal. This difference in expression is most easily explained by X-linkage, but the possibility of a sex-influenced autosomal allele cannot be ruled out.

The litters produced by the original bitch show a significant deficiency of males, assuming a 1:1 ratio of sexes. Various estimates of the sex ratio for dogs at birth have been calculated and they differ for different breeds[3]. No estimate is available for the Australian shepherd. The estimates for all breeds indicate a relative excess of males, and so our calculations are probably conservative. The male deficiency for the original bitch would fit a 1:2 ratio of males to females, which could be interpreted to indicate that one of her two X chromosomes carried a gene that was lethal to hemizygous males, as a separate trait from the syndrome of defects. However, it is unlikely that a second male lethal gene is present in this family. It would be expected that half of her daughters also would receive this chromosome and show similar sex-ratio distortion in their male progeny, but this effect was not seen. Also, average litter size for the dam was higher than for her daughters, which would not be expected if an in utero lethal were acting. In addition, the two supplemented litters from the original dam did not have a deficiency of males (in fact, they had a 2:1 male:female ratio), so this deficiency of males indeed may be spurious.

Affected dams had a higher ratio of affected female pups than the unaffected dams, which may show the effects of modifying genes on the expression of the affected phenotype in carrier females. The data also seemed to show that vitamin-mineral supplementation enhances the penetrance or expressivity of the gene.

This syndrome of skeletal defects, including cleft palate and polydactyly, is most likely inherited as an X-linked incompletely dominant allele, lethal in the hemizygous condition. The syndrome has not been reported previously and may be unique to this family. We propose the gene symbol *Sl* for this skeletal lethal trait. Viable males are not expected to produce this trait. Unaffected females may be inapparent carriers, but those that fail to produce affected sons are likely to be noncarriers and will not pass the defective allele to offspring. Dietary supplementation with vitamins and minerals may increase the penetrance of the allele in females. Of interest is that the original dam is a homozygous merle, and the possibility that the syndrome arose as a part of the instability of that locus must be considered[5,6]. Further study of families arising from homozygous merles should provide information about that possibility.

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