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Deafness prevalence and pigmentation and gender associations in dog breeds at risk

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Abstract

Hearing function was tested in dogs from breeds at risk for pigment-associated congenital sensorineural deafness – Dalmatian, English setter (ES), English cocker spaniel (ECS), bull terrier (BT), Australian cattle dog (ACD), whippet, Catahoula leopard dog, and Jack Russell terrier. Deafness prevalence was highest in Dalmatians and lowest in ECS. Phenotype correlation studies were performed in breeds with >100 brainstem auditory evoked responses (BAER) tested subjects. No gender differences were observed. No differences were seen between black- and liver-spotted Dalmatians, among the ES roan colour varieties, among the ECS parti varieties, or among the ACD colour varieties. Blue eyes were positively associated and patches were negatively associated with deafness in the Dalmatian. Blue eyes were also associated with deafness in the ES and ECS. White BT were more likely than coloured BT to be deaf. Having one or more parent's ear deaf was positively associated with deafness in Dalmatians, ES, and ECS.

Keywords: Deafness; Dog; Pigment; Piebald; Melanocyte

1. Introduction

Canine deafness is diagnosed with increasing frequency, primarily as a result of heightened awareness about the disorder among owners, breeders, and clinicians. The aetiology can be hereditary or acquired. The most commonly seen forms of deafness are (1) congenital sensorineural deafness, seen most often in dogs with white pigmentation, (2) conductive deafness associated with otitis externa and/or media, and (3) later-onset sensorineural deafness associated with otitis interna, chronic otitis media, ototoxicity (i.e., from gentamicin), noise trauma (gun fire), or presbycusis in older dogs (Strain, 1996, 1999).

Deafness and its association with pigmentation patterns in dogs have been described in published reports as early as 1896, when Rawitz noted an association between deafness and blue eyes in a white dog. Congenital deafness has been observed in at least 80 breeds (Table 1), in which hereditary components are assumed but not proven for most breeds, and in which the deafness in most but not all breeds is associated with skin pigmentation genes conferring either white pigmentation or light vs dark patterns. Limited scientific examination of phenotypic markers predictive of deafness has been performed until recently (Strain et al., 1992). There is little current dispute that white pigmentation is a risk factor for deafness in the dog and other animal species, but the mechanisms by which this risk ensues are not yet fully understood.

The canine locus or gene designated by the symbol *S* is perhaps the one most associated with deafness. The *S* locus affects the distribution pattern of pigmented and white (non-pigmented) areas on the body (Little, 1957; Sponenberg and Rothschild, 2001), while other genes determine the actual colour of the pigmented areas. The *S* locus has at least four alleles. The dominant allele *S* is known as self or non-spotted, and produces a completely pigmented body surface, although minor areas, of white may be present on the feet or thorax. The s^i allele produces Irish spotting and presents with only a few white areas that are usually on locations such as the thorax,

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Table 1
Breeds with reported congenital sensorineural deafness[a]

Akita	Dogo Argentino	Pit bull terrier
American bulldog	English bulldog	Pointer
American-Canadian shepherd	English cocker spaniel	Presa Canario
American Eskimo	English setter	Puli
American Staffordshire terrier	Foxhound	Rhodesian ridgeback
Australian cattle dog	Fox terrier	Rat terrier
Australian shepherd	French bulldog	Rottweiler
Beagle	German shepherd	Saint Bernard
Bichon Frise	Great Dane	Samoyed
Border collie	Great Pyrenees	Schnauzer
Borzoi	Greyhound	Scottish terrier
Boston terrier	Havanese	Sealyham terrier
Boxer	Ibizan hound	Shetland sheepdog
Bulldog	Italian greyhound	Shih Tzû
Bull terrier	Jack Russell terrier	Shropshire terrier
Cardigan Welsh Corgi	Kuvasz	Siberian husky
Catahoula leopard dog	Labrador retriever	Soft coated Wheaten terrier
Cavalier King Charles spaniel	Löwchen	Springer spaniel
Chihuahua	Maltese	Sussex spaniel
Chinese crested	Miniature pinscher	Tibetan spaniel
Chow chow	Miniature poodle	Tibetan terrier
Cocker spaniel	Mongrel	Toy fox terrier
Collie	Norwegian dunkerhound	Toy poodle
Coton de Tulear	Nova Scotia duck tolling retriever	Walker American foxhound
Dalmatian	Old English sheepdog	West Highland white terrier
Dappled dachshund	Papillon	Whippet
Doberman pinscher	Perro de Carea Leonés	Yorkshire terrier

[a] From personal observations by the author, communications from breeders, and as summarized in Strain (1996).

feet, face, or head. The s^p allele produces piebald spotting and produces significantly more white on the body surface than Irish spotting, including the limbs, while the s^w or extreme-white piebald allele is associated with an even greater extent of white pigmentation, including the ears and base of the tail. These alleles are listed in order of decreasing epistasis. Although the specific allele responsible for white pigmentation is not known for all breeds, the Basenji and bloodhound are examples of homozygous Irish spotting, the beagle is an example that is usually homozygous piebald, and the Dalmatian and white bull terrier are examples of homozygous extreme-white piebald. Because the epistatic alleles are recessive they must be present in pairs to produce their white pattern, but it is possible for a dog to carry one copy each of two of the recessive alleles, as may occur with Boston terriers that are normally $s^i s^i$ but that may on occasion be $s^i s^p$ or $s^i s^w$ (Little, 1957).

The alleles s^p and s^w are present in the great majority of breeds recognized to be subject to congenital deafness when the identity of pigmentation genes is known, but the white-producing allele is often not known. The recessive alleles produce white by acting on differentiation and/or migration of melanocyte precursor cells from the neural crest during embryogenesis. It is likely that additional genes regulate the expression of the three recessive *S* alleles, such that, for example, strong expression of s^w in Dalmatians results in blue irises from suppression of melanocytes in the eye, and weak expression of s^w results in the large pigmented area on some Dalmatians known as a patch, which is present at birth when the rest of the puppy is still white.

A second pigmentation locus associated with deafness is that designated by *M*, often known by the name associated with the pattern of the dominant allele, merle. Homozygosity of the recessive allele (*mm*) produces uniform pigmentation, while the heterozygous merle (*Mm*) produces dappling or alternate body areas of fully pigmented coat and pale eumelanic or even white coat. Homozygous merles (*MM*) are usually nearly solid white, and in some breeds may be deaf, blind with microphthalmic eyes, and sterile. Dogs heterozygous for *M* are variable in their likelihood of deafness. The harlequin gene (H^H) has been identified as a dominant modifier of the merle gene in Great Danes that is lethal when present in the homozygous state (Sponenberg, 1985); harlequin Danes are at relatively high risk for deafness, while other colour variants are less likely to be affected. Great Dane dogs may carry *M*, *m*, H^H, s^i, s^p, or s^w gene alleles in various combinations, as well as other potential modifier genes, which provides an indication of the complexity of pigmentation genetics in various dog breeds.

Other genes reported to produce white or light coat colour in dogs – flecking, ticking, dilution with fawn – do not appear to be associated with deafness. Albinism, in which melanocytes are present but one of the enzymes responsible for melanin production (tyrosinase) is

absent or diminished, does not usually have an association with deafness. Forms of hereditary deafness also exist in dog breeds without an association with white pigmentation (e.g., Doberman pinscher, Shropshire terrier), where different mechanisms produce deafness. Those breeds are not considered here.

Most studies of congenital deafness in dogs have focused on the Dalmatian. Two publications based on data from approximately 1000 animals each (Holliday et al., 1992; Strain et al., 1992) documented the prevalence of deafness in Dalmatians in the US to be approximately 8% bilateral deafness and 22% unilateral deafness, or 30% affected. Data from European countries have reported lower prevalence rates (Muhle et al., 2002; Wood and Lakhani, 1997), possibly due to the disallowance of blue eyes in the Dalmatian breed standard of most European countries; efforts to breed away from blue eyes reduced deafness prevalence in Dalmatians in Norway (Greilbrokk, 1994).

No significant association with deafness was seen in the Dalmatian for completeness of eye rim pigmentation, completeness of nose pigmentation, spot colour, spot size, or heaviness of spot markings (Strain et al., 1992). Significant associations with hearing status were observed for patch, iris colour, and eye tapetal pigment. Dogs with a patch had a significant negative association with the presence of deafness, and dogs with either a blue iris or absent tapetal pigment had a positive association with the presence of deafness. The Dalmatian patch appears to result from weak expression of the extreme-white piebald gene, while the eye pigment anomalies result from strong expression of the gene, and hence absent melanocytes in the iris and tapetum. Data from many studies have demonstrated in numerous species that pigment-associated deafness is the result of absent melanocytes in the stria vascularis of the cochlea, which leads to early postnatal degeneration of the stria and secondary degeneration of the cochlear hair cells and neurons – the consequence again of strong expression of the gene.

Few similar phenotype-deafness studies have been reported for other breeds, except for the Norwegian dunkerhound, in which unilateral or bilateral deafness has been reported to occur in 75% of all white animals (Foss, 1981), and the dappled (merle) dachshund, where 18.2% were reported to be bilaterally deaf and 36.4% were unilaterally deaf (Reetz et al., 1977). In both breeds the prevalence of deafness in coloured or non-dappled dogs was not documented but is low.

This study documents deafness prevalence in eight dog breeds in which pigment-associated congenital sensorineural deafness occurs – Dalmatian, English setter (ES), English cocker spaniel (ECS), bull terrier (BT), Australian cattle dog (ACD), whippet, Catahoula leopard dog, and Jack Russell terrier (JRT). Pigment associations with deafness are documented based on phenotype data collected at the time of hearing testing in those breeds with >100 tested subjects. Pedigree information was not available for most subjects. All of the breeds are carriers of recessive alleles of the *S* gene. The Dalmatian is s^w, ES is s^p but also occasionally s^w, the ECS (based on the cocker spaniel) can be either s^p or s^w, the white BT is s^w while the coloured BT is s^i, and the whippet can be s^i, s^p or s^w (Little, 1957); the alleles carried by the ACD, Catahoula, and JRT are not known.

An unresolved issue in Dalmatian studies has been that of gender. Several studies have reported a greater percentage of deaf females over males (Greilbrokk, 1994; Holliday et al., 1992; Wood and Lakhani, 1997, 1998), while others (Famula et al., 2000; Hayes et al., 1981; Strain et al., 1992) have found no difference. Accordingly, gender distribution of deafness was also examined, applying the statistical power of very large data sets to provide more confidence for statistical associations.

2. Materials and methods

2.1. Animals

Hearing results and phenotype data were recorded from dogs ($N = 11{,}300$) during the period 1986–2002. The data were collected in clinic settings or at dog shows from owners or breeders seeking documentation of the absence of deafness, or because of suspicions of hearing deficits. Data are reported in this study from eight breeds. Data reported here for dogs in the ECS, BT, ACD, whippet, Catahoula, and JRT breeds were collected entirely by the author. Dalmatian data ($N = 5333$) were compiled from tests by the author ($N = 2665$) and also data compiled by the Dalmatian Club of America's research committee from other test sites, including (1) Phoenix, AZ ($N = 947$, Dr. D. Levesque), (2) northern California ($N = 1181$, Drs. H. Nelson and C. Sousa), and (3) a combination of other sites that heavily concentrated on data from Chicago, IL ($N = 538$, Dr. G. Mayer and others). These Dalmatian data incorporate the data ($N = 1031$) from this author's 1992 study (Strain et al., 1992). English setter data ($N = 3656$) were compiled from tests by the author ($N = 662$) and also data compiled by the English Setter Association of America (ESAA) hearing registry (personal communication, Mrs. Jane Wooding, English Setter Association of America, Redding, CT, USA) ($N = 2994$ after excluding tests by GMS), representing data from across the United States with a small number from other countries. English setter data were analyzed in combination and separately by data subset (GMS, ESAA) because of possible sampling bias (see below).

2.2. Hearing testing

Brainstem auditory evoked response (BAER) tests were performed using established methods (Strain, 1997; Strain et al., 1991). Bone stimulation BAER tests (Strain et al., 1993) were also performed by the author on dogs that tested as deaf while using air-conducted stimuli if any basis existed for the presence for conduction deafness, such as on-going or chronic otitis. Many of the other participating test sites did not perform bone stimulation BAER recordings. Hearing status was classified as hearing (B), unilaterally deaf (U), or bilaterally deaf (D) based on BAER results. Analyses of data was done by default using a trichotomous model (B, U, D), but analyses with a dichotomous model (B, D) where both D and U results were considered to be D were performed to reduce variance when results were unclear. No attempt was made to distinguish between hereditary and acquired origins when deafness was diagnosed, but the percentage with acquired deafness was assumed to be very small. The hearing status (B, U, D, or unknown) of both parents was also recorded.

2.3. Pigmentation phenotypes

Gender and iris colour measurements (pigmented or blue) were recorded from animals in all breeds. Other pigmentation phenotype measures were recorded that varied by breed. These included (Table 2): (1) the presence of a patch in Dalmatians, (2) colour varieties in those breeds where some white is always present, such as spot colour in Dalmatians, parti colour varieties of English cocker spaniels, and roan colours of English setters, and (3) white vs non-white pigmentation in those breeds where those varieties exist, including parti vs solid colour in English cocker spaniels and white vs coloured in bull terriers. Parti is a term used to indicate non-solid coloured dogs with small areas of white. The greatest diversity in colour varieties was seen in English cocker spaniels, where pigment data were collected from five roan parti varieties, four white and colour parti varieties, and five solid colour varieties (Table 2). Association analyses with pigmentation varieties in the Catahoula, whippet, and JRT breeds were not performed because fewer than 100 subjects had been BAER tested.

2.4. Statistical analysis

Deafness prevalence data and association analyses were performed using the χ^2 test with SAS statistics software (PROC FREQ) as described elsewhere (SAS/STAT User's Guide, Version 8, 1999). Results are reported as significantly associated, rather than significantly correlated, since the χ^2 statistic was used instead of a correlation coefficient to determine significance. The χ^2 test creates contingency tables for comparisons of observed frequencies and expected frequencies. When the number of observations within any table cell is less than one, or the number of observations are less than five in more than 20% of the cells, the χ^2 test is considered to possibly be inaccurate. Under these circumstances the discrepancy was resolved using Fisher's exact probability test. Analyses of the ES data subsets also utilized Cochran–Mantel–Haenszel statistics to assess conditional independence of the data subsets GMS and ESAA (Agresti, 1996). The individual data points in these analyses cannot be considered strictly to be independent, since various familial relationships were present (litter mate, father–daughter, etc). However, since pedigree relationships were not known for most subjects, pedigree-based analyses (Famula et al., 2000; Wood and Lakhani, 1997) could not be performed and the data were by necessity considered independent.

3. Results

3.1. Prevalence

The presence of congenital deafness is reported in 80 dog breeds at the time of this report (Table 1). Prevalence data (Table 3) for the dogs from the eight breeds examined in this study ranged from a high of 29.9% affected (unilaterally deaf and bilaterally deaf) in the Dalmatian breed to a low of 6.9% affected in the ECS. Prevalence data for the whippet, Catahoula, and JRT are reported, but the rates are not necessarily represen-

Table 2
Pigment-associated phenotypic measures for selected breeds

Breed	Pigmentation phenotype measures
Dalmatian	variety colour: black; liver patch: absent; present
English setter	variety colour: blue roan; orange roan; tricolour
English cocker spaniel	variety colour: parti colour: blue roan; orange roan; liver roan; blue roan and tan; liver roan and tan parti colour: black and white; orange and white; liver and white; black, white and tan (tri) solid colour: solid black; solid red; solid liver; solid golden; solid black and tan
Bull terrier	variety colour: white; coloured
Australian cattle dog	variety colour: blue; red; blue and tan; blue, black and tan

Table 3
Deafness prevalence in 11,300 dogs from selected breeds

Breed	*N*	Bilaterally hearing[a]	Unilaterally deaf (U)	Bilaterally deaf (D)	Total deaf [U + D]	Ratio [U/(U + D)]
Dalmatian	5333	70.1% (3740)	21.9% (1167)	8.0% (426)	29.9% (1593)	0.733
English setter[b]	3656	92.1% (3368)	6.5% (236)	1.4% (52)	7.9% (288)	0.819
GMS	662	87.6% (580)	10.3% (68)	2.1% (14)	12.4% (82)	
ESAA	2994	93.1% (2788)	5.6% (168)	1.3% (38)	6.9% (206)	
English cocker spaniel	1136[c]	93.1% (1057)	5.9% (67)	1.1% (12)	6.9% (79)	0.848
Parti coloured	1067	93.0% (992)	5.9% (63)	1.1% (12)	7.0% (75)	
Solid	60	98.3% (59)	1.7% (1)	0.0% (0)	1.7% (1)	
Bull terrier	665[c]	89.0% (592)	9.9% (66)	1.1% (7)	11.0% (73)	0.904
White	346	80.1% (277)	18.0% (62)	2.0% (7)	19.9% (69)	
Coloured	311	98.7% (307)	1.3% (4)	0.0% (0)	1.3% (4)	
Australian cattle dog	296	85.5% (253)	12.2% (36)	2.4% (7)	14.5% (43)	0.837
Whippet[d]	80	98.8% (79)	0.0% (0)	1.3% (1)	1.3% (1)	–
Catahoula leopard dog[d]	78	37.2% (29)	23.1% (18)	39.7% (31)	62.8% (49)	–
Jack Russell terrier[d]	56	83.9% (47)	7.1% (4)	8.9% (5)	16.1% (9)	–

[a] Percentage and (*N*).
[b] Values collected by GMS and from the English Setter Association of America hearing registry.
[c] *N* values for colour varieties do not sum to the *N* values for all dogs in a breed due to missing data.
[d] Insufficient numbers of animals tested for percentages to be reliable.

tative for those breeds due to the low numbers of dogs tested. Many Catahoula tests were performed on animals when owners sought testing services because deafness was suspected, while most whippet tests were performed at national breed specialty dog shows where the percentage of affected animals present might be expected to be lower than the overall breed prevalence. Prevalence data for ECS and BT were further broken down by major colour categories, and the data for ES were broken down by source, since it was anticipated that data submitted to a closed voluntary registry might under-represent numbers of affected animals. The prevalence of deafness in the GMS ES data subset was significantly higher than in the ESAA subset ($df = 2$, $\chi^2 = 22.753$, $p < 0.0001$).

The ratio of unilaterally deaf to total affected ranged from a high of 0.904 in BT to a low of 0.733 in Dalmatians (Table 3). This ratio reflects the proportion of deaf dogs within a breed with unilateral deafness that can go undetected in the absence of BAER testing (i.e., 73.3% in the Dalmatian).

3.2. Gender

For the five breeds analyzed, no gender difference in deafness prevalence was seen ($p > 0.05$) for the Dalmatian, BT, or ACD (Table 4). Chi-square analyses showing no gender difference for the BT and ACD data were confirmed using Fisher's exact test. To reduce variability, the hearing data for those two breeds were also collapsed from a trichotomous model (B, U, D) to a dichotomous model (B, D) so that either U or D was classified as D. The χ^2 analysis showed no significant relationship between gender and deafness prevalence in BT and ACD. A significant relationship ($p = 0.035$) was seen for the ECS breed with a trichotomous model, but under a dichotomous model the significance was no longer present ($p = 0.067$, Table 4). While the percentages of English cockers with bilateral deafness were similar for females and males (0.44% and 0.62%, respectively), the percentages with unilateral deafness had a wider gap (3.99% vs 1.68%). No significant gender difference was present in either ES data subset, but the combined data indicated a highly significant difference ($p = 0.014$). However, the Cochran–Mantel–Haenszel statistic documented that the significance was not real ($p = 0.323$). In addition, the sex difference in ES hearing data was not significant when considered as a dichotomous trait ($p = 0.601$). Despite the absence of significant gender differences, the percentage of total affected females exceeded the percentage of total affected males in the Dalmatian, ECS, BT, ACD, and ESAA ES data, but not the GMS ES data.

3.3. Coat pigmentation

The coat pigmentation varieties that are unrelated to the genes that produce white were not significantly associated with deafness (Table 5). There were no statistical differences in deafness prevalence between black- and liver-spotted Dalmatians (χ^2 $p = 0.890$); lemon and tricolour spotted Dalmatians were not included in the analysis because of the rarity of these dogs (0.4% in this data base). There were no differences among blue, orange, or tricolour roan ES (χ^2 $p = 0.853$), or among the four colour varieties of ACD (χ^2 $p = 0.176$, Fisher's exact test $p = 0.106$). In the parti ECS, two subtypes of parti can be distinguished: parti roan, and parti white and colour (i.e., white and black, Table 2). Solid English cockers are presumed to be genetically *SS* or Ss^x, where

Table 4
Gender differences[a] in deafness prevalence

Breed	*N* (female/male)	% female/% male[b]	Hearing comparison[c]	df	χ^2	*p*	*F p*[d]
Dalmatian	5329 (2668/2661)	31.18/28.45	B/U/D	2	4.821	0.090	
English setter	3654 (1938/1716)	8.10/7.44	B/U/D	2	8.506	0.014	
			B/D	1	0.274	0.601	
GMS	661 (372/289)	11.83/13.15	B/U/D	2	4.579	0.101	
ESAA	2993 (1566/1427)	7.22/6.52	B/U/D	2	4.987	0.083	
English cocker spaniel	1129 (629/500)	7.95/5.20	B/U/D	2	6.714	0.035	
			B/D	1	3.353	0.067	
Bull terrier	655 (396/259)	12.63/8.88	B/U/D	2	2.636	0.268[e]	0.256
			B/D	1	2.219	0.136	
Australian cattle dog	296 (171/125)	15.20/13.60	B/U/D	2	1.212	0.545[e]	0.522
			B/D	1	0.150	0.699	

[a] Chi-square statistic.
[b] Percent total affected females/percent total affected males.
[c] B, bilaterally hearing; U, unilaterally deaf; D, bilaterally deaf. For B/D comparisons, D, unilaterally and bilaterally deaf combined.
[d] Fisher's exact test.
[e] Excess cells had expected counts less than 5; χ^2 may not be a valid test.

Table 5
Coat pigmentation differences in deafness prevalence

Breed	Pigment comparison	Hearing comparison[a]	*N*	df	χ^2	*p*	*F p*[b]
Dalmatian	black/liver spots	B/U/D	5256 (4332/924)	2	0.232	0.890	
	patch absent/present	B/U/D	5283 (4814/469)	2	98.661	<0.0001	
English setter	blue/orange/tricolour roan	B/U/D	3650 (958/2395/297)	4	1.349	0.853	
English cocker spaniel	parti roan/parti white and colour/solid	B/U/D	1127 (888/179/60)	4	3.537	0.472[c]	0.633
	parti/solid	B/U/D	1127 (1067/60)	2	2.646	0.266[c]	0.394
	parti/solid	B/D	1127 (1067/60)	1	2.597	0.107[c]	0.178
	parti roan/parti white and colour	B/U/D	1067 (888/179)	2	0.847	0.655	
Bull terrier	white/coloured	B/U/D	657 (311/346)	2	57.810	<0.0001[c]	<0.0001
	white/coloured	B/D	657 (311/346)	1	57.717	<0.0001	
Australian cattle dog	blue/blue and tan/blue, black and tan/red	B/U/D	293 (71/18/124/80)	6	8.952	0.176[c]	0.106

[a] B, bilaterally hearing; U, unilaterally deaf; D, bilaterally deaf. For B/D comparisons, D, unilaterally and bilaterally deaf combined.
[b] Fisher's exact test.
[c] Excess cells had expected counts less than 5; χ^2 may not be a valid test.

s^x is one of the three recessive alleles. No significant differences were seen when deafness prevalence was compared between the parti roan and parti white and colour varieties (χ^2 $p = 0.655$).

Significant differences were seen for coat pigmentation varieties linked to white genes. Dalmatians without a patch were statistically more likely to be deaf than Dalmatians with a patch (χ^2 $p < 0.0001$.) White BT were statistically more likely to be deaf than coloured BT (χ^2 $p < 0.0001$, Fisher's exact test $p < 0.0001$). With the dichotomous model for hearing, the difference was significant without the need for a Fisher's exact test comparison (χ^2 $p < 0.0001$). Deafness prevalence comparisons among the ECS varieties of parti roan, parti white and colour, and solid were not significant (χ^2 $p = 0.472$, Fisher's exact test $p = 0.633$). When the two parti varieties were collapsed into a single parti variety, there was no difference between parti and solid (χ^2 $p = 0.266$, Fisher's exact test $p = 0.394$). Examining the data as a dichotomous model also did not show a difference in deafness prevalence in parti vs solid ECS (χ^2 $p = 0.107$, Fisher's exact test $p = 0.178$). Since there was only one unilaterally deaf dog and no bilaterally deaf dogs among the 60 solid ECS in the data base (Table 3), the parti vs solid comparisons may still be uncertain.

3.4. Iris colour

The prevalence of blue eyes (one or both) in the Dalmatian was comparatively high at 10.6%, while in ES it was 0.5%, in ECS it was 0.4%, and in BT it was 0.2% (Table 6). Dalmatian irises were classified as two brown eyes (BrBr), one brown and one blue (BrBl), or two blue eyes (BlBl); in liver-spotted Dalmatians the pigmented iris colour was more gray than brown, but any non-blue pigmented iris was defined as brown for

Table 6
Iris colour differences in deafness prevalence

Breed	Colour comparison[a]	*N*	df	χ^2	*p*	*F p*[b]
Dalmatian	BR BR/BR BL/BL BL	5203 (4650/407/146)	4	159.928	<0.0001	
	BR/BL	5204 (4650/554)	2	159.089	<0.0001	
English setter (GMS)[c]	BR/BL	649 (646/3)	2	18.927	<0.0001[d]	0.012
English cocker spaniel	BR BR/BR BL/BL BL	1122 (1118/3/1)	4	92.796	<0.0001[d]	0.009
	BR/BL	1112 (1118/4)	2	21.866	<0.0001[d]	0.035
Bull terrier	BR BR/BR BL/BL BL	659 (658/0/1)	2	8.999	0.011[d]	0.100

[a] BR BR, two brown irises; BR BL, one blue iris; BL BL, two blue irises; BR, two brown irises; BL, one or two blue irises.
[b] Fisher's exact test.
[c] Data from GMS subset only because the ESAA subset did not record iris colour data.
[d] Excess cells had expected counts less than 5; χ^2 may not be a valid test.

purposes of analysis. Deafness prevalence (B/U/D) was statistically related to iris colour (BR BR/BR BL/BL BL), with blue-eyed dogs more likely to be deaf ($p < 0.0001$, Table 6). Collapsing the iris colour categories into BR vs BL(BL = BR BL + BL BL) also demonstrated a significant association between deafness prevalence and iris colour ($p < 0.0001$). Of the 554 Dalmatians with one or two blue eyes (Table 6), 179 (32.3%) were unilaterally deaf and 102 (18.4%) were bilaterally deaf, or 50.7% were affected.

English setter iris colour, which was only recorded as BR vs BL, was also statistically associated with deafness prevalence (χ^2 $p < 0.0001$, Fisher's exact test $p = 0.012$). Only three of the 649 ES with recorded iris colour had one or two blue eyes (Table 6): of these three, one was unilaterally deaf and one was bilaterally deaf. English cocker spaniel iris colour (BR BR/BR BL/BL BL) was statistically associated with deafness prevalence (χ^2 $p < 0.0001$, Fisher's exact test $p = 0.009$); the association was also significant when iris colour categories were collapsed into BR vs BL (χ^2 $p < 0.0001$, Fisher's exact test $p = 0.035$). Only four of the 1122 ECS had one or two blue eyes (Table 6): three with one blue eye had normal hearing, and one with two blue eyes was bilaterally deaf.

Bull terrier iris colour did not exhibit a consistent significant association with deafness prevalence (χ^2 $p = 0.011$, but Fisher's exact test $p = 0.100$). However, none of the 659 BT had just one blue eye and only one had two blue eyes, a white BT with unilateral deafness, so the comparison may still be uncertain. None of the ACD had a blue eye.

3.5. Parental hearing status

A highly significant association between hearing status and parent hearing status was seen for the Dalmatian, ES, and ECS breeds (Table 7), where dogs had a higher likelihood of deafness if one or both parents were also affected. No significant associations were seen for the BT or ACD breeds. However, the Fisher's exact test for these comparisons gave the warning of a large percentage of data missing (very few subjects had known parental hearing status), suggesting that these results may still be uncertain.

4. Discussion

The number of dog breeds reported here with congenital deafness (Table 1) improves upon previous listings (Strain, 1996, 1999). Although it is not exclusively the case, the vast majority of these breeds carry white pigmentation or merle genes. Notable exceptions are the Doberman pinscher and the Puli.

Table 7
Parental hearing status differences in deafness prevalence

Breed	Parental hearing status[a]	*N*	df	χ^2	*p*	*F p*[b]
Dalmatian	BB/BU/UU	3454 (2624/804/26)	4	49.163	<0.0001	
	B/D	3455 (2624/831)	2	44.531	<0.0001	
English setter	BB/BU/UU	1899 (1850/48/1)	4	13.644	0.009[c]	0.010
	B/U	1899 (1850/49)	2	12.978	0.002[c]	0.004
English cocker spaniel	BB/BU/BD	475 (449/25/1)	4	15.662	0.004[c]	0.007
	B/D	475 (449/26)	2	14.663	0.0007[c]	0.004
Bull terrier	BB/BU/UU	252 (233/13/6)	4	2.173	0.704[c]	0.516
	B/D	278 (233/45)	2	1.005	0.605[c]	0.809
Australian cattle dog	BB/BU	92 (81/11)	2	0.751	0.687[c]	0.493

[a] BB, both parents bilaterally hearing; BU, one unilaterally deaf parent; BD, one bilaterally deaf parent; UU, both parents unilaterally deaf; B, both parents bilaterally hearing; D, at least one deaf ear between parents; U, at least one unilaterally deaf parent but no bilaterally deaf parents.
[b] Fisher's exact test.
[c] Excess cells had expected counts less than 5; χ^2 may not be a valid test.

It is clear that deafness is hereditary in the Dalmatian, and that pigmentation is an important component as in other species carrying white (Steel, 1995; Steel and Barkway, 1989), but the exact mechanism of inheritance is still not determined (Famula et al., 2000; Muhle et al., 2002; Wood and Lakhani, 1997). Presumably the same association between deafness and pigmentation is true of the other breeds of this study, supported by the findings presented here, but these breeds have not seen the benefit of similar studies.

The observed prevalence of deafness was highest in the Dalmatian breed, with 29.9% affected. Individual Dalmatian registrations reported from American Kennel Club records in the years 2000 and 2001 were 3084 and 2139, respectively, and the numbers of litter registrations were 1262 and 764 (Bielski, 2002). Assuming an average litter size of eight (Treen and Treen, 1980), the estimated total registrations for the two years were 13,180 and 8251 Dalmatians. Although registrations underestimate the total number of dogs and some litter-registered puppies are eventually registered as individuals, the totals still suggest, based on the deafness prevalence rates reported here, that 3941 and 2467 newly registered Dalmatians were deaf in one or both ears in those two years, giving an estimate of the impact of deafness in this breed. These numbers also underestimate prevalence because puppies from back-yard breeders and puppy mills typically have higher deafness prevalence rates than those from mainstream breeders due to indiscriminate breeding and failure to test the hearing of breeding stock. The other breeds of this study had registration rates in the US at lower but similar numbers to Dalmatians (Bielski, 2002).

In the absence of a genetic marker for the gene or genes responsible for pigment-associated deafness, the remaining strategy to reduce deafness prevalence has been to not breed affected dogs and to breed away from pedigrees with high prevalence rates. Unfortunately, unilaterally deaf dogs exhibit little if any behavioural evidence of their defect, so affected dogs and bitches that are not BAER tested as puppies or prior to being bred will, when bred, continue to increase the prevalence of the disorder. The percentage of affected dogs with unilateral deafness was 73% for Dalmatian, 82% for ES, 84% for ACD, 85% for ECS, and 90% for BT (Table 3); in the absence of BAER testing these are the percentages of affected animals potentially available for breeding, and hence worsening the prevalence of deafness.

Gender differences in deafness prevalence were not seen in the Dalmatian, BT, or ACD, and differences were not seen in the ECS or ES if hearing was considered to be a dichotomous trait (Table 4). The presence of significant differences in ES or ECS with the trichotomous model for hearing may reflect an imbalance in the affected animals, since the association between gender and deafness lost significance when the trichotomous model was replaced by the dichotomous model (ECS $p = 0.601$, ES $p = 0.067$). It is unclear that a trichotomous model better represents this disorder, since unilateral deafness is logically considered to be incomplete expression of deafness that in its complete expression affects both ears, and use of a trichotomous model may insert additional unjustifiable variance. One study (Famula et al., 1996) suggested that different genes controlled the hearing status for each ear; however, this premise is not supported by similar mechanisms for other bilateral structures in the body, and the authors have since moved to consider other models for inheritance of deafness (Famula et al., 2000).

No significant gender effect was seen in either the GMS or the ESAA data subsets of the ES deafness data, yet when they were combined a highly significant difference was seen. The Cochran–Mantel–Haenszel statistic for conditional independence demonstrated this to be an example of Simpson's paradox (Agresti, 1996), where the significance seen in conditional associations (the ES data subsets) is reversed in marginal associations (subsets combined). The non-significant result of the CMH statistic ($p = 0.323$) showed that the significance seen with the combined data sets was false and artifactual, and no significant gender difference existed. In addition, significance was not seen in ES with a dichotomous model. These findings may be a reflection of the significant difference for prevalence between the two data subsets; when the analysis controlled for test site (GMS vs ESAA) the gender difference lost significance. The difference in prevalence between the subsets may be a result of the fact that submission of BAER results to the ESAA hearing registry is voluntary, which likely inserts a sampling bias against inclusion of affected ES.

Although several investigators have reported a significant excess in deafness in Dalmatian females compared to males (Greilbrokk, 1994; Holliday et al., 1992; Wood and Lakhani, 1997, 1998), it is unclear from a consideration of possible genetic mechanisms why such an effect might occur. It has been suggested (Famula et al., 2001) that these differences may be reflective of the fact that BAER testing is voluntary and as a result a population sampling bias may have been introduced that selectively revealed deafness more frequently in females than males. Wood, who found a higher deafness prevalence in females (Wood and Lakhani, 1997), utilized generalized logistic methods to model hearing in 1234 Dalmatians in the UK, simultaneously taking into account testing site, coat colour, gender, parental hearing, litter effects, as well as interaction effects among all of the variables. Significant effects were seen for gender and for litter interaction effects, among others. It is difficult to explain why gender effects were seen in that one study, but not in this study with more than four times the number of animal subjects. It may be possible that founder effects are being seen in the UK or that

relative geographical restriction effects have had an impact. It is also unclear how litter effects and other variables might interact with gender to influence the distribution of affected animals beyond what is seen from direct prevalence comparisons. One other small study also reported an excess of males affected (Anderson et al., 1968). The overall conclusion that must be drawn from the findings of this study is that there is no gender difference in deafness prevalence in the breeds studied. The eventual identification of the molecular genetic cause of this form of deafness may resolve the issue of gender. Dialogue on this issue will doubtless continue.

Pigmentation varieties that are not determined by the genes responsible for white colour were not significantly associated with deafness. Spot colour in the Dalmatian (black, liver), roan varieties in ES (orange, blue, tricolour), the two subtypes of parti colour in ECS (parti roan vs. parti white and colour), and the four colour varieties in ACD (blue, red, blue and tan, blue, black and tan) showed no significant association (Table 5). This outcome was expected because the responsible genes – primarily the *B-b* pair (black/liver), but also the *A*, *C*, *D*, and *E* series (Little, 1957) – are not considered as risk factors for deafness. However, colour variations resulting from genes producing white did show significant associations with deafness: patched Dalmatians were less likely to be deaf than unpatched, as reported in previous studies (Cattanach, 1999; Famula et al., 2000; Greilbrokk, 1994; Strain et al., 1992), and white BT were more likely to be deaf than coloured BT. Surprisingly, no difference was detected between roan and solid ECS, but only one of 60 solid ECS was affected, so the statistical results may be uncertain.

In addition, suppression of iris pigmentation by white genes was significantly associated with deafness in the Dalmatian, ES, and ECS (Table 6). Significance was not seen in BT, but only one dog of 659 was affected, again making the findings uncertain. Blue eyes in non-Dalmatian breeds were rare, but carried a high association with deafness when it did occur: two of three blue-eyed ES were affected, one of four ECS was affected, and one of one BT was affected. For comparison, 50.7% of blue-eyed Dalmatians were affected. In these breeds, the occurrence of one or two blue eyes should suggest a strong likelihood that deafness is present. Significant associations between blue eyes and deafness in Dalmatians have been reported in numerous other studies (Cattanach, 1999; Famula et al., 2000; Greilbrokk, 1994; Holliday et al., 1992; Muhle et al., 2002; Strain et al., 1992).

Together, the above combine to reinforce the postulate that deafness in these breeds is closely linked to the recessive alleles of the pigmentation locus *S*, and that phenotype indicators of strong expression of the gene, such as blue eyes, or indicators of weak expression of the gene, such as the Dalmatian patch, convey information on the likelihood of deafness. Studies have shown that deafness in the Dalmatian has high heritability, and that the inheritance is best modelled as a single major locus (Famula et al., 2000; Muhle et al., 2002). The findings of this study of significant association between deafness and parental hearing status (Table 7) support this. However, the single major locus inheritance is not best modelled as a simple recessive Mendelian autosome (Famula et al., 2000; Gaillard et al., 2002; Juraschko et al., 2003; Muhle et al., 2002), which explains the difficulty of tracking deafness in pedigrees of affected animals.

Significant progress is being made in the identification of genes responsible for deafness in humans and mice (Steel and Bussoli, 1999; Steel and Kros, 2001). With progress being made in sequencing the canine genome (Ostrander et al., 2000) and the recent availability of a set of microsatellite markers spanning the canine genome (Cargill et al., 2002; Richman et al., 2001), it is now possible to begin whole-genome screens of DNA from dogs in pedigrees with deafness (Cargill et al., 2001). Once the gene defect responsible for pigment-associated deafness is identified, greater progress in reducing deafness prevalence will be possible through utilization of DNA testing.

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