Prevalence of congenital sensorineural deafness in a population of client-owned purebred kittens in the United Kingdom

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Abstract

Background: Data about congenital sensorineural deafness (CSD) in white blue-eyed cats derive mainly from research colonies, and information about client-owned cats is limited.

Objectives: To describe the prevalence of CSD in a client-owned population of white purebred kittens and colored littermates in the United Kingdom.

Animals: One hundred thirty-two solid white client-owned purebred kittens and 61 colored littermates, 6 to 21 weeks of age.

Methods: Retrospective (56 cases) and prospective (137 cases) study. Hearing was assessed by brainstem auditory evoked response testing, and the entire litter was tested.

Results: Congenital sensorineural deafness was diagnosed only in solid white kittens, with a prevalence of 30.3% (15.9% bilateral, 14.4% unilateral). The prevalence of CSD was significantly higher in white kittens with 1 (44.4%) or 2 (50%) blue irises than in those without blue irises (22.2%). Kittens with at least 1 blue iris were 3.2 times more likely to have CSD than kittens without blue irises. In solid white kittens, CSD was diagnosed in 7 of 15 (46.7%) Turkish Vankedisi, 8 of 18 (44.0%) Maine Coon, 18 of 41 (43.9%) Norwegian Forest, 3 of 11 (27.3%) British Shorthair, 2 of 12 (16.7%) Devon Rex, 2 of 12 (8.3%) Persian, 1 of 21 (4.8%) Russian, and 0 of 2 Sphinx. The prevalence of CSD was significantly different in Norwegian Forest, Maine Coon, and Turkish Vankedisi kittens compared with Persian or Russian kittens.

Conclusion and Clinical Importance: We identified a high prevalence of CSD in a population of client-owned purebred white kittens in the United Kingdom and suggest differences in breed-specific prevalence of CSD.

KEYWORDS
blue eyes, blue irises, blue-eyed, cat, feline, hearing, white

1 | INTRODUCTION

Congenital sensorineural deafness (CSD) in white blue-eyed cats is a well-known phenotype investigated since the 19th century as a model for CSD in humans.1-10 In the embryo, melanoblasts derived from the
neural crest migrate to target organs, including the skin and eyes, where they mature in to melanocytes and determine pigmentation patterns.\textsuperscript{1,11,12} In the inner ear, melanocytes in the stria vascularis are responsible for maintaining the high potassium concentration within endolymph, which is crucial in the creation of the endocochlear potential necessary for activation of the hair cells.\textsuperscript{1,12-14} Migration and function of melanocytes are regulated by numerous genes connected with hearing.\textsuperscript{11,15-20} Congenital sensorineural deafness has been reported in breeds of cats that carry the autosomal dominant white gene (W).\textsuperscript{21} A pleiotropic gene with polygenic effects was suggested as the most likely model of inheritance of CSD in white cats.\textsuperscript{22} Recent research identified an insertion of feline endogenous retrovirus 1 in intron 1 of the KIT gene as responsible for dominant white and white spotting coat phenotype in cats and showed an association between CSD and the genotype of the triallelic KIT variant.\textsuperscript{23,24}

The gold standard test to assess hearing function in domestic animals is the brainstem auditory evoked response (BAER) test, which is an electrodagnostic test based on the response of peripheral and central hearing pathways to an auditory stimulus consisting of a series of clicks.\textsuperscript{25} The responses are fully mature by 20 days of age in cats.\textsuperscript{12}

The majority of the published data on CSD in cats is based on research colonies used as a model for CSD in humans, and the results in terms of prevalence of the disease are not applicable to client-owned cats because of different breeding strategies. In addition, the majority of these studies were published 4 to 6 decades ago, and more recent data are needed. In the research colonies of crossbred white cat, the overall prevalence of CSD evaluated by BAER testing varied between 50% and 96%, being higher in cats with blue irises and more commonly bilateral than unilateral.\textsuperscript{5-8} To date, a single study has evaluated the hearing status by BAER testing in a population of 84 client-owned purebred white cats in Germany, including both kittens and adult cats of different breeds presented for prebreeding screening.\textsuperscript{26} This study detected a CSD prevalence of 20.2%, with unilateral and bilateral CSD being almost equally represented. Also in this study, the prevalence of CSD was 44% in cats with 2 blue irises, 20% in cats with 1 blue iris, and 19% in cats without blue irises.\textsuperscript{26} Information about prevalence of CSD in specific breeds is limited. The prevalence of CSD in Norwegian Forest (18%, \( n = 329 \)), Maine Coon (17%, \( n = 134 \)), and Turkish Angora (11%, \( n = 474 \)) has been anecdotally reported,\textsuperscript{22} but hearing status was not always based on BAER testing, and likely missed cases of unilateral deafness.

The aim of our study was to report the overall and breed-specific prevalence of unilateral and bilateral CSD evaluated by BAER testing and its association with iris color in a UK population of client-owned purebred white kittens and colored littermates.

2 | MATERIALS AND METHODS

2.1 | Animals

Ethics approval was obtained from the institution’s ethics committee. Inclusion criteria were (i) purebred kittens belonging to a litter with at least 1 solid (ie, completely) white kitten undergoing BAER testing in both ears; (ii) BAER testing performed in the entire litter; (iii) detailed description of coat and iris color of the kittens; and (iv) no history of ear disease or topical administration of potentially ototoxic drugs. Kittens that underwent BAER testing between January 2004 and December 2013 were included retrospectively. Kittens that underwent BAER testing between January 2014 and April 2018 were included prospectively. The details about parents’ coat color, iris color, and hearing status were recorded when available.

2.2 | BAER testing

In all kittens, BAER testing was performed in both ears by the same operator using an electrodiagnostic unit (Medelec Synergy N-EP 5-channel system; Oxford Instruments Medical, Old Woking, United Kingdom). No kitten needed sedation for the procedure (Figure 1). Subcutaneous stainless steel electrodes were positioned using the following montage: the positive electrode at the vertex, the negative electrode rostral to the tragus, and the ground electrode at the level of the external occipital protuberance. The auditory stimulus consisted in a series of clicks of 0.1 millisecond in duration delivered via unshielded audiometric headphones (model TDH49P, Oxford Instruments Medical, Old Woking, United Kingdom) at the rate of 30/s and intensity of 80 dB normal hearing level. The BAER was obtained by averaging 512 recordings of 10 milliseconds. Filters were set at the cutoff frequencies of 100 Hz and 3 kHz. If no responses were obtained at 80 dB, the stimulus was increased to 100 dB. When questionable BAER was obtained from 1 ear, the test was repeated while providing a masking noise to the contralateral ear at an intensity of 20 dB below the click stimulus. A kitten was defined as normal if waves I to V were visible at 80 dB in the traces from both ears (Figure 2), unilaterally deaf if no waves were visible at 80 and 100 dB in 1 ear (Figure 3), and bilaterally deaf if the latter finding was obtained from both ears (Figure 4).

2.3 | Statistical methods

Analyses were performed using XLStat (Addinsoft, Long Island City, NY). Differences in prevalence of CSD, for example, among breeds, between
male and female kittens and among kittens with 1, 2, or no blue irises were tested for significance using chi-squared tests ($\alpha = 0.05$). Subsequently, a multivariate logistic regression model was built to assess the effects of breed and iris color as independent variables on the likelihood of CSD. The effect of breed was first assessed using logistic regression ($\alpha = 0.05$) with stepwise backward elimination (threshold for retention
Breeds were entered into the model in a binary fashion (i.e., belonging to a particular breed = 1 and not belonging to that breed = 0). Retained breeds then were assessed alongside iris color (presence of blue irises) in the final model (threshold for retention \( P \leq 0.10 \)).

### RESULTS

A total of 193 kittens (56 retrospectively and 137 prospectively) from 50 litters were included in the study. There were 132 solid white kittens, including 41 of 65 Norwegian Forest (15 litters), 21 of 28 Russian (6 litters), 18 of 35 Maine Coon (7 litters), 15 of 18 Turkish Vankedisi (6 litters), 12 of 16 Persian (6 litters), 12 of 16 Devon Rex (5 litters), 11 of 12 British shorthair (4 litters), and 2 of 3 Sphynx (1 litter). The remaining 61 pigmented kittens were either fully pigmented (43) or white spotted (18). The median age at the time of BAER testing was 10 weeks (range, 6-21 weeks); 99 kittens were males (70 white) and 94 were females (62 white). The prevalence of CSD was not significantly different between male and female kittens (\( \chi^2 = 0.089, P = .76 \)).

None of the 61 colored kittens (fully pigmented or white spotted) was unilaterally or bilaterally deaf. The overall prevalence of CSD in the 132 solid white kittens was 30.3% (15.9% bilateral and 14.4% unilateral; Table 1). Unilateral CSD affected the left ear in 9 of 19 (47%) kittens and the right ear in 10 of 19 (53%) kittens.

### TABLE 1

| Breed           | Number of kittens | Solid white kittens, n (%) | Solid white kittens with blue irises, n (%) | Solid white kittens with CSD, n (%) |
|-----------------|-------------------|----------------------------|--------------------------------------------|-------------------------------------|
|                 |                   | 1                          | 2                                          | Unilateral  | Bilateral | Total   |
| Norwegian Forest| 65                | 41 (63)                    | 8 (19.5)                                  | 6 (14.6)   | 9 (21.95) | 9 (21.95) | 18 (43.9) |
| Maine Coon      | 35                | 18 (51.4)                  | 3 (16.7)                                  | 8 (44.4)   | 2 (11.1)  | 6 (33.3)  | 8 (44.4)  |
| Turkish Vankedisi| 18               | 15 (83.3)                  | 3 (20)                                    | 9 (60)     | 4 (26.7)  | 3 (20)    | 7 (46.7)  |
| British Shorthair| 12              | 11 (91.7)                  | 1 (9)                                     | 0          | 2 (18.2)  | 1 (9.1)   | 3 (27.3)  |
| Russian         | 28                | 21 (75)                    | 0                                         | 0          | 0         | 1 (4.8)   | 1 (4.8)   |
| Persian         | 16                | 12 (75)                    | 1 (8.3)                                   | 0          | 1 (8.3)   | 0         | 1 (8.3)   |
| Devon Rex       | 16                | 12 (75)                    | 1 (8.3)                                   | 1 (8.3)    | 1 (8.3)   | 1 (8.3)   | 2 (16.7)  |
| Sphinx          | 3                 | 2 (66.7)                   | 1 (50)                                    | 0          | 0         | 0         | 0         |
| Total           | 193               | 132 (68.4)                 | 18 (13.6)                                 | 24 (18.2)  | 19 (14.4) | 21 (15.9) | 40 (30.3) |
Details on breed-specific prevalence of unilateral or bilateral CSD and coat and iris color are reported in Table 1. None of the 61 pigmented kittens (fully pigmented or white spotted) had blue irises. Eighteen (13.6%) solid white kittens had 1 blue iris and 24 (18.2%) kittens had 2 blue irises. The prevalence of CSD was 50.0% in solid white kittens with 2 blue irises (25.0% unilateral and 25.0% bilateral), 44.4% in solid white kittens with 1 blue iris (22.2% unilateral; and 22.2% bilateral) and 22.2% in solid white kittens without blue irises (10.0% unilateral and 12.2% bilateral). The side of the unilateral CSD matched the side of the single blue iris in 2 of 4 kittens. The prevalence of CSD was significantly higher in cats with either 1 or 2 blue irises than in cats without any blue irises ($\chi^2 > 3.85, P \leq .05$), but there was no significant difference in CSD prevalence between kittens with 1 or 2 blue irises ($\chi^2 = 0.13, P = .72$). Therefore, for further analyses, only 2 categories were considered: no blue irises and at least 1 blue iris.

When comparing pairs of breeds, the prevalence of CSD was significantly higher in Norwegian Forest kittens compared to Russian ($\chi^2 = 10.01, P = .002$) and Persian ($\chi^2 = 5.11, P = .02$) kittens. The same was true for Maine Coon kittens compared to Russian ($\chi^2 = 8.60, P = .003$) and Persian ($\chi^2 = 4.47, P = .03$) kittens and for Turkish Vankedisi kittens compared to Russian ($\chi^2 = 8.89, P = .003$) and Persian ($\chi^2 = 4.70, P = .03$) kittens. Sphynx kittens were excluded from these comparisons because they were represented by only 2 individuals. In the logistic regression model, the Norwegian Forest breed was significantly associated with the presence of CSD when compared to non-Norwegian Forest breeds grouped together and therefore was retained in the final model ($\chi^2 = 4.71, P = .03$; Hosmer-Lemeshow $\chi^2 = 1.13, P = .25$). None of the other breeds was significantly associated with CSD when compared to kittens not belonging to that breed grouped together. In the final model, containing binary iris color (0 or at least 1 blue iris) and Norwegian Forest breed compared to non-Norwegian Forest breeds ($\chi^2 = 13.41, P = .001$; Hosmer-Lemeshow $\chi^2 = 3.46, P = .33$), both variables were significantly associated with CSD ($P = .004$ and $P = .03$, respectively). Solid white kittens with at least 1 blue iris were 3.2 times more likely to have CSD compared with those without blue irises (95% confidence interval [CI], 1.5-7.2) and Norwegian Forest solid white kittens were 2.5 times more likely to have CSD compared with non-Norwegian Forest solid white kittens (95% CI, 1.1-5.7).

The details of the parents’ coat color, iris color, and hearing status could be obtained only for the 86 solid white kittens included prospectively. All these kittens resulted from breeding a solid white cat with either a fully pigmented (66/86 cases) or a white spotted (20/86 cases) cat. White kittens born from crossing a solid white parent with a white spotted parent did not have a higher prevalence of CSD compared to white kittens obtained by crossing a solid white parent with a fully pigmented parent ($\chi^2 = 0.0109, P = .92$). In 2 cases, no information about the parents’ iris color was available. For all the other kittens, at least 1 of the parents had pigmented irises. The other parent had pigmented irises in 44 cases, 1 blue iris in 18 cases, 2 blue irises in 20 cases, and unknown iris color in 2 cases. The prevalence of CSD in kittens derived from crossing 2 parents with no blue irises was not significantly different compared to that when 1 of the parents had at least 1 blue iris ($\chi^2 = 0.0398, P = .84$). Information about the hearing status of the parents was provided for the 86 prospectively included solid white kittens. The hearing status was never assessed with BAER testing in both parents. In 67 of 86 solid white kittens, 1 of the parents had a BAER testing performed (66 normal and 1, a Norwegian Forest dam, unilaterally deaf), whereas the other parent was clinically normal without BAER test confirmation. In the other 19 of 86 white kittens, neither of the parents was tested. Fifteen of these 19 kittens were born from 2 clinically normal parents. The last 4 kittens were obtained from a clinically deaf (without BAER confirmation) Norwegian Forest sire mated with a clinically normal dam, and 3 of them were deaf (1 unilateral and 2 bilateral).

4 | DISCUSSION

We investigated the prevalence of CSD in client-owned purebred white kittens and non-white littermates in the United Kingdom. The results identified a high prevalence of CSD in the population studied and suggested the presence of breed-specific differences. The overall prevalence of CSD in solid white kittens was higher than that previously reported including client-owned purebred white cats in Germany (30.3% versus 20.2%), which simply could reflect 2 different populations in terms of breeds, breeding lines, and inclusion criteria. Indeed, for example, in the German population, there were proportionally many more British Shorthair and fewer Norwegian Forest kittens compared to our population. In addition, in the previous study, the population included both kittens and adult cats aged 2 to 108 months at the time of BAER testing, and their littermates were not routinely tested.26

In our study, the prevalence of CSD was found to be >40% in solid white kittens of some breeds (Norwegian Forest, Maine Coon, Turkish Vankedisi) compared with 27.3% in British Shorthair and <17% in other investigated breeds (Russian, Persian, Devon Rex). These differences were found to be statistically significant when comparing Norwegian Forest, Maine Coon, or Turkish Vankedisi kittens with either Russian or Persian kittens. Although the higher prevalence of blue irises in the Norwegian Forest, Maine Coon, and Turkish Vankedisi kittens compared with other breeds could in itself justify the higher prevalence of CSD detected in these 3 breeds, the prevalence of CSD was not significantly different between Norwegian Forest (43.9%) and Turkish Vankedisi (46.9%) kittens despite a significantly lower prevalence of blue irises in the former (34.1%) compared with the latter (80.0%) breed. When modeling the Norwegian Forest breed compared to non-Norwegian Forest breed and iris color as independent variables in multivariate logistic regression analysis, both variables were found to be significantly associated with higher risk of CSD. The fact that a significant association between CSD and breed was not identified for Maine Coon or Turkish Vankedisi when compared to the remainder of the population might be related to the lower number of cases in these 2 breeds compared to the Norwegian Forest breed. Unfortunately, despite adequate overall sample size, the low number...
of kittens in some of the included breeds represented a limitation of the study, preventing us from performing additional more detailed analyses and suggesting cautious interpretation of our results.

Interestingly, some of the breed-specific prevalence of CSD obtained in our study was similar to what can be extrapolated from a previous publication. Analyzing the raw data reported in the previous study, the British Shorthair was the most commonly represented breed (31/84 cats) with a prevalence of CSD of 16.1% (27.3% in our study), whereas only 6 Norwegian Forest cats were included, 4 of which had unilateral or bilateral CSD. Also, 5 of 14 (35.7%) Maine Coon cats included in the previous study were diagnosed with unilateral or bilateral CSD (44.4% in our study), whereas only 1 of 9 (11.1%) Persian cats had this phenotype (8.3% in our study). Considering the results of these 2 studies, further research into the prevalence of CSD in different breeds in larger populations is warranted.

If these differences in prevalence of CSD among breeds are confirmed in larger studies, it would mean that the overall prevalence of deafness in white purebred populations of cats would be affected by the breeds included, subsequently supporting the benefit of a breed-specific approach in the investigation of CSD in white cats. The breed-specific prevalence of CSD detected in solid white Norwegian Forest (43.9%) and Maine Coon (44.4%) kittens in our study is markedly higher when compared to previously reported data on larger populations (18% and 17%, respectively), but the hearing status in that population was not always based on BAER testing, therefore potentially missing unilaterally deaf cats.

In agreement with previous studies, the prevalence of CSD was significantly higher in solid white cats with at least 1 blue iris compared to cats without blue irises, with an odds ratio of 3.2 (95% CI, 1.5-7.2) similar to that found previously (3.7; 95% CI, 0.9-18.4). However, unlike that study, we found no significant difference in the prevalence of CSD when comparing kittens with 1 or 2 blue irises. According to our data, and in agreement with that previously reported unilateral and bilateral CSD were almost equally represented. In studies on research colonies of cross-breed white cats, unilateral and bilateral CSD were almost equally represented. However, unlike that study, we found no significant difference in the prevalence of CSD when comparing kittens with 1 or 2 blue irises.

In conclusion, the results of our study suggest a high prevalence of CSD in purebred client-owned solid white kittens of the included breeds in the United Kingdom. Different breed-associated prevalences of CSD might exist, supporting the benefit of a breed-specific approach to this disease. Since 2016, the Governing Council of the Cat Fancy has made it mandatory for a white cat in the United Kingdom to have a BAER test certifying normal hearing status in order to be included in the active register (the register of cats suitable to be bred from), which is a first important step for improving breeding strategies and decreasing propagation of the disease. In our study, individuals were tested as kittens while still under the care of the breeder, and no kitten required sedation, supporting the noninvasive and well-tolerated nature of the procedure when performed by an experienced operator. The BAER testing of kittens allows early detection of CSD before an individual cat is included in any breeding program.

CONFLICT OF INTEREST DECLARATION
Authors declare no conflict of interest.

OFF-LABEL ANTIMICROBIAL DECLARATION
Authors declare no off-label use of antimicrobials.

INSTITUTIONAL ANIMAL CARE AND USE COMMITTEE (IACUC) OR OTHER APPROVAL DECLARATION
Ethics approval was obtained from the Animal Health Trust Clinical Research Ethics Committee (AHT 37_2013).

HUMAN ETHICS APPROVAL DECLARATION
Authors declare human ethics approval was not needed for this study.

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REFERENCES
1. Ryugo DK, Menotti-Raymond M. Feline deafness. Vet Clin North Am Small Anim Pract. 2012;42:1179-1207.
2. Strain GM. Hearing disorders in cats. J Feline Med Surg. 2017;19:276-287.
3. Bree W. White cats with blue eyes are always deaf. Mag Nat Hist. 1829:1:178.
4. Darwin C. On the Origin of Species by Means of Natural Selection. London: Murray; 1859:18.
5. Bergsma DR, Brown KS. White fur, blue eyes, and deafness in the domestic cat. J Hered. 1971;62:171-185.
6. Bosher SK, Hallpike CS. Observations on the histological features, development and pathogenesis of the inner ear degeneration of the deaf white cat. Proc R Soc Lond B Biol Sci. 1965;162:147-170.
7. Delack JB. Hereditary deafness in the white cat. Compend Contin Educ Pract. 1984;6:609-619.
8. Mair IW. Hereditary deafness in the white cat. Acta Otolaryngol Suppl. 1973;314:1-48.
9. Rebillard M, Pujol R, Rebillard G. Variability of the hereditary deafness in the white cat. II. Histology. Hear Res. 1981;5:189-200.
10. Ryugo DK, Cahill HB, Rose LS, Rosenbaum BT, Schroeder ME, Wright AL. Separate forms of pathology in the cochlea of congenitally deaf white cats. Hear Res. 2003;181:73-84.
11. Lin JY, Fisher DE. Melanocyte biology and skin pigmentation. Nature. 2007;445:843-850.
12. Strain GM. Deafness in Dogs and Cats. Wallingford, UK: Cabi; 2011.
13. Steel KP, Barkway C. Another role for melanocytes: their importance for normal stria vascularis development in the mammalian inner ear. Development. 1989;107:453-463.
14. Takeuchi S, Ando M, Kakigi A. Mechanism generating endocochlear potential: role played by intermediate cells in stria vascularis. Biophys J. 2000;79:2572-2582.
15. Yamaguchi Y, Brenner M, Hearing VJ. The regulation of skin pigmentation. J Biol Chem. 2007;282:27557-27561.
16. Schmutz SM, Berryere TG. Genes affecting coat colour and pattern in domestic dogs: a review. Anim Genet. 2007;38:539-549.
17. Price ER, Fisher DE. Sensorineural deafness and pigmentation genes: melanocytes and the Mitf transcriptional network. Neuron. 2001;30:15-18.
18. Strain GM. The genetics of deafness in domestic animals. Front Vet Sci. 2015;2:9.
19. Tachibana M. Cochlear melanocytes and MITF signaling. J Invest Dermatol Symp Proc. 2001;6:95-98.
20. Kaelin CB, Barsh GS. Genetics of pigmentation in dogs and cats. Annu Rev Anim Biosci. 2013;1:125-156.
21. Strain GM. Cat breeds with congenital deafness [Internet]. https://www.lsu.edu/deafness/catbreeds.htm. Accessed August 18, 2018.
22. Geigy CA, Heid S, Steffen F, Danielson K, Jaggy A, Gaillard C. Does a pleiotropic gene explain deafness and blue irises in white cats? Vet J. 2007;173:548-553.
23. David VA, Menotti-Raymond M, Wallace AC, et al. Endogenous retrovirus insertion in the KIT oncogene determines white and white spotting in domestic cats. G3 (Bethesda). 2014;4:1881-1891.
24. Frischknecht M, Jagannathan V, Leeb T. Whole genome sequencing confirms KIT insertions in a white cat. Anim Genet. 2015;46:98.
25. Scheifele PM, Clark JG. Electrodiagnostic evaluation of auditory function in the dog. Vet Clin North Am Small Anim Pract. 2012;42:1241-1257.
26. Cvejic D, Steinberg TA, Kent MS, Fischer A. Unilateral and bilateral congenital sensorineural deafness in client-owned pure-breed white cats. J Vet Intern Med. 2009;23:392-395.
27. General breeding policy [Internet]. https://www.gccfcats.org/Breeding-Information/GCCF-Breeding-Policy. Accessed August 18, 2018.

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