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Breed, Coat Color, and Hair Length as Risk Factors for Hyperthyroidism in Cats

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Background: Hyperthyroidism is very common in older cats, but the etiopathogenesis is poorly understood. Decreased risk of hyperthyroidism has been reported in certain colorpoint breeds, and this observation previously has been hypothesized to result from relatively greater tyrosine availability for thyroid hormone production because of limited ability to convert tyrosine to melanin pigment. However, studies investigating a potential link between coat pigmentation and risk of hyperthyroidism are limited.

Objective: To identify associations between coat phenotype and hyperthyroidism by investigation of breed, coat color, and hair length as risk factors for the disease.

Animals: Data were used from 4,705 cats aged ≥10 years, referred to a single veterinary teaching hospital (2006–2014) in the United Kingdom.

Methods: Retrospective, epidemiological, cross-sectional study using Bayesian multivariable logistic regression to assess risk factors for hyperthyroidism.

Results: Burmese (odds ratio [OR], 0.01; 0.00–0.23; $P = .004$), Tonkinese (OR, 0.05; 0.00–0.95; $P = .046$), Persian (OR, 0.21; 0.10–0.44; $P < .001$), Siamese (OR, 0.27; 0.12–0.61; $P = .002$), Abyssinian (OR, 0.04; 0.00–0.74; $P = .031$), and British shorthair (OR, 0.47; 0.28–0.79; $P = .004$) breeds had decreased risk of hyperthyroidism compared to domestic shorthairs. Longhaired, nonpurebred cats (OR, 1.30; 1.03–1.64; $P = .028$) were at increased risk of hyperthyroidism. Coat color/pattern was not associated with hyperthyroidism in nonpurebred cats.

Conclusions and Clinical Importance: We identified decreased risk of hyperthyroidism in the Tonkinese, Abyssinian, and British shorthair breeds, identified an association between risk of hyperthyroidism and hair length, and confirmed decreased risk in Burmese, Siamese, and Persian breeds. Additional studies are warranted to further investigate these findings.

Key words: Cat; Pigment; Tyrosinase; Tyrosine.

Hyperthyroidism affects up to 10% of geriatric cats and is associated with increased mortality and deleterious effects on several organ systems.[1–3] The etiopathogenesis is suspected to be multifactorial and is poorly understood, but the condition in cats appears histopathologically and functionally analogous to toxic nodular goiter (TNG) in humans.[4–6] Factors that restrict thyroid hormone availability resulting in chronic stimulation of the thyroid gland by thyrotropin (TSH) have been described as a potential mechanism for development of thyroid autonomy in humans with TNG, and a similar mechanism may play a role in cats.[7] Epidemiological studies have identified Siamese, Himalayan, and Burmese breeds to be at decreased risk of developing hyperthyroidism.[1,8,9] The characteristic colorpoint coats of these breeds result from temperature-sensitive mutations in the tyrosinase gene which limit conversion of the amino acid tyrosine to melanin pigment except at the cooler extremities.[10] In addition to functioning as a precursor of melanin, tyrosine is an essential precursor of thyroid hormone. It has been hypothesized that the protective effect observed in colorpoint breeds may be related to the mutation in tyrosinase that leads to relatively greater tyrosine availability for thyroid hormone production.[11] In that study, tyrosine concentrations were measured in relatively few cats and no difference was seen in hyperthyroid versus euthyroid, or in heavily versus lightly pigmented animals. The authors commented that the study was underpowered. Further studies, to either support or refute their hypothesis, are lacking.

Abbreviations:

CI	confidence interval
DLH	domestic longhair
DSH	domestic shorthair
EPR	electronic patient records
GCCF	Governing Council of the Cat Fancy
IQR	interquartile range
MLR	multivariable logistic regression
OR	odds ratio
T4	thyroxine
TNG	toxic nodular goitre
TYRP1	tyrosinase related protein 1
TSH	thyrotropin/thyroid-stimulating hormone

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This study was performed at the Royal Veterinary College, London, UK.

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There is evidence to suggest that dietary concentrations of tyrosine recommended for inclusion in commercially produced diets for cats have been inadequate to maintain dark coloration hair in black cats.[12,13] Published nutrient requirements for tyrosine in cat foods historically have not been distinguished from those of its precursor phenylalanine.[14] However, concentrations of melanin in cat hair have been shown to be positively related to plasma tyrosine concentrations, even when phenylalanine concentrations were high enough to support growth.[12,13,15] This finding is in contrast to studies in humans that have shown that intracellular conversion of phenylalanine to tyrosine provides the majority of l-tyrosine for melanogenesis.[16] If dietary tyrosine is marginally sufficient in cats, then the degree of coat pigmentation may be impacted by relative tyrosine availability and result in associations between coat color and the risk of hyperthyroidism. Similarly, other coat phenotypes, such as hair length, might be associated with risk of hyperthyroidism if they affect pigmentation requirement and relative tyrosine availability, but published studies investigating this possibility are limited. Evidence in support of a link between tyrosine availability and hyperthyroidism may give rise to further research into a potential avenue for disease prevention by dietary tyrosine supplementation and the possible need for a review of recommendations regarding requirements of this nutrient in commercial cat foods.

Our objective was to identify associations between coat phenotype and feline hyperthyroidism by investigation of breed, coat color, and hair length as risk factors for this disease. Based on the assumptions that coat color reflects melanin concentration and that degree of pigmentation may affect relative tyrosine availability for thyroid hormone production, it was hypothesized that cats with lighter (less pigmented) coat phenotypes, such as colorpoints or those with white markings, are at lower risk of hyperthyroidism than cats with darker (more highly pigmented) coat colors and that cats with short hair are at lower risk of hyperthyroidism than are cats with long hair.

Materials and Methods

This retrospective, epidemiological, cross-sectional study of cats was undertaken at a single veterinary teaching hospital (Queen Mother Hospital for Animals, Royal Veterinary College, Hatfield, Hertfordshire, United Kingdom). Electronic patient records (EPRs) were searched to obtain recorded data regarding breed, coat color, age, sex, neuter status for all cats aged ≥10 years of age that were seen between January 2006 and June 2014. Because of potential differences in patient population and limited access to full previous medical history, and for the purposes of data analysis, cats that had visited the emergency first-opinion service out of hours were differentiated from those referred to the Queen Mother Hospital for Animals by their primary practice for a second opinion.

Case Identification

To classify cats as either hyperthyroid or euthyroid, a search of EPRs was conducted for the following keyword terms: "hyperthyroid," "hyperthyroidism," "methimazole," "felimazole," "carbimazole," "vidalta," "neomercazole," and "thyroidectomy,"; the treatments: "radioactive iodine therapy," "methimazole," "felimazole," "carbimazole," and "vidalta," or coded diagnoses of "hyperthyroidism" or "radioactive iodine therapy," and case records containing any of these terms were reviewed. Cats were classified as hyperthyroid if they met any of the following criteria: a history of treatment with radioactive iodine, thyroidectomy, treatment with antithyroid medication containing carbimazole or methimazole, or a diagnosis of hyperthyroidism recorded by the teaching hospital or by the referring veterinary surgeon. All remaining patients were classified as euthyroid.

Data Coding

Breeds recognized by the Governing Council of the Cat Fancy (GCCF) were coded as "purebred." Cats listed as GCCF purebred cross or stated as crossbreed were coded as "purebred cross." Domestic shorthair (DSH) and domestic longhair (DLH) cats were coded as "nonpurebred," with cats recorded as domestic medium hairs or domestic semilonghair included with the DLH group. In nonpurebreds, coat color data were used to record the overall coat color and pattern using the following color groups: "black," "blue/gray," "brown" (including dark brown/chocolate/light brown/cinnamon), "lilac/fawn," "red/ginger,", "cream," "tabby," "tortoiseshell," "colorpoint/point/pointed," and "white," or any of the previously listed colors "and white." Coat color data also were used to classify base pigment color as "black" (which included black/blue/gray coat colors), "brown" (which included brown/dark brown/chocolate/light brown/cinnamon/lilac/fawn), or "red" (which included red/ginger/cream). Additionally, coat color was classified as "dilute" if blue/gray/lilac/fawn/cream, and "nondilute" for all other color groups excluding tortoiseshell, tabby, colorpoint, and white, for which the base pigment was categorized as unknown. Nonpurebreds additionally were coded according to whether they had "all white," "some white," or "no white," markings and whether they were "shorthaired" or "longhaired." Breeds not recognized by the GCCF, other colors, and groups where $n < 10$ were excluded from the analysis. Age was classified in 5 categorical groups (10 years, 11–12 years, 13–14 years, 15–17 years, and ≥18 years) where age ranges were selected by visual assessment of the distribution.

Statistical Analyses

Data were analyzed using a computerized statistical software package.[a] Bayesian multivariable logistic regression (MLR) with flat priors was used to investigate the following variables as risk factors for hyperthyroidism in 2 separate analyses:

1 Breed analysis: Breed, age, sex, neuter status and referral/first-opinion status were evaluated as risk factors for hyperthyroidism in all cats.
2 Coat color/hair length analysis: Coat color/pattern, base pigment, color dilution, presence of white markings, hair length, age, sex, neuter status, and referral/first-opinion status were evaluated as risk factors in nonpurebred cats only.

Color and hair length analysis was carried out in nonpurebreds only, to avoid confounding in purebreds where coat color and hair length may be fixed by breed standards and where inconsistent use of terms for coat color variants among breeds precluded analysis of colors in purebreds. Bayesian MLR methodology was employed to overcome any issue of complete separation and inability to calculate odds ratios (ORs) in groups that lacked hyperthyroid cases and to facilitate analysis of group sizes as small as $n = 10$. For risk factors with ≥3 categories, the likelihood ratio test was used

to assess overall significance. Variables where $P < .2$ in univariable analyses were entered into a multivariable model constructed using manual, backward, stepwise elimination until all remaining variables in the final model were significant to the level of $P \leq .05$. Odds ratios for variables were reported with 95% confidence intervals (CIs).

Results

Study Population Descriptive Statistics

Data from 4,705 cats were available for analysis. Of these, 975 cats were classified as hyperthyroid, giving a prevalence of hyperthyroidism of 20.7% (95% CI, 17.3–51.2%) in cats ≥10 years. The majority of cats were nonpurebred (83.0%, n = 3,903), 14.9% (n = 702) were GCCF breeds, 1.3% (n = 63) were purebred crosses, and the remainder (0.8%, n = 37) were non-GCCF breeds. Of the purebred crosses, 7.9% (5 of 63) were recorded as Siamese crosses, but for the remainder, individual breeds were not stated. Just over one-third of cats (34.8%, n = 1,637) had been seen by the first-opinion out-of-hours service. Overall, the median age of cases was 13 years (interquartile range [IQR], 11–15). Female cats comprised 47.8% (2,233 of 4,675) of the study population, and 94.4% (4,440 of 4,705) of cats overall were stated as neutered. Sex was not stated for 0.5% (30 of 4,705) of cats, and coat color was not recorded for 3.4% (131 of 3,903) of nonpurebreds; these cats were excluded from the risk factors analyses.

Of all cats that were classified as hyperthyroid, 65.0% (634 of 975) had a coded diagnosis of hyperthyroidism on their EPR, and 57.0% (556 of 975) had a total thyroxine (T4) concentration measured while at the hospital that was above the reference range for the hospital laboratory (19–65 nmol/L). Just over one-half of the hyperthyroid cats (53.1%, 518 of 975) had received radioactive iodine treatment at the hospital, 10.9% (106 of 975) were prescribed antithyroid medication by the hospital, and 0.1% (1 of 975) had total T4 concentration >40 nmol/L in combination with a free T4 concentration >40 pmol/L. Additionally, 25.7% (251 of 975) were classified as hyperthyroid solely based on review of the history stating that a previous diagnosis of hyperthyroidism had been made.

In the separate analysis of coat color/pattern, hair length, age, sex, neuter status, and referral status in nonpurebred cats, the median age was 13 years (IQR, 11–15), 48.4% (1,815 of 3,752) were females, and 94.8% (3,577 of 3,772) were stated as neutered. Of 3,772 nonpurebred cats where coat color was recorded, 2.5% (96 of 3,772) either had unclassifiable coat color or were of a group size where n < 10, and sex was not known for 0.5% (20 of 3,772); these cats were excluded from further analyses. Of the 3,656 nonpurebreds included in the risk factors analyses, it was not possible to classify base pigment in 39.3% (1,435 of 3,656) and color dilution in 56.7% (2,072 of 3,656) of cats.

Analysis of Breed, Age, Sex, Neuter Status, and Referral Status in All Cats. The results for the univariable and multivariable analyses of all cats are shown in Table 1. Breed, age, sex, neuter status, and referral status had $P < .2$ in the univariable analysis and subsequently were evaluated in the multivariable model. These variables all remained significantly associated with hyperthyroid risk in the final model. Burmese, Tonkinese, Persians, Siamese, Abyssinians, British shorthairs (BSH), and purebred crosses had decreased risk of hyperthyroidism compared to DSHs. Domestic longhairs showed increased risk of hyperthyroidism compared to DSHs. Females had increased risk of hyperthyroidism compared to males, and neutered cats showed increased risk compared to intact cats. When compared to 10-year-old cats, increased risk of hyperthyroidism was found in cats aged 11–17 years, but this was not observed in cats ≥18 years old. Cats seen by the hospital on a referral basis were more likely to be hyperthyroid than cats that had been seen by the first-opinion emergency service. Breed standards for hair length and whether breeds were fixed for colorpoint coat color are indicated in Table 1 for reference. Of the breeds showing decreased risk of hyperthyroidism, Siamese, Burmese, and Tonkinese breeds are fixed for colorpoint coats, BSH and Persian cats are accepted with colorpoint coats, and Abyssinians do not have colorpoint coats. Although coat color was not examined as a variable in this model, it was noted that 60.3%, (76 of 126) of BSH in the study were a dilute color, 72.3% (55 of 76) of which were blue. More than half (57.1%, 4 of 7) of the GCCF breeds that did not show decreased risk of hyperthyroidism were longhaired breeds, whereas only 1 of the 6 protected breeds (Persian) was longhaired.

Analysis of Coat Color/Pattern, Base Pigment, White Markings, Color Dilution, Hair Length, Age, Sex, Neuter Status, and Referral Status in Nonpurebred Cats. The results from the univariable and multivariable analysis of nonpurebred cats are shown in Table 2. In the univariable logistic regression, white markings and color dilution were not associated with hyperthyroidism. Coat color/pattern, base pigment, age, sex, age, hair length, neuter status, referral status, and base pigment had $P < .2$ and were entered into multivariable analyses. In the univariable analysis, the base pigment of tortoiseshell cats was found to be associated with increased risk of hyperthyroidism ($P = .047$) compared to cats with black base pigment, but this finding did not retain significance in the multivariable analyses. In the final multivariable model, longhaired cats were found to be at greater risk of hyperthyroidism than were shorthaired cats. Age, sex, and referral status in the nonpurebred cats were associated with thyroid status in accordance with the results from the analysis of all cats (Table 1). However, neuter status did not retain significance in the nonpurebred multivariable model.

Discussion

This observational study aimed to identify associations between the coat phenotype of cats and risk of developing hyperthyroidism. In addition to supporting previously published findings regarding breed, age, and sex, our study newly identified 3 additional breeds at

Table 1. Breed, age, sex, neuter status, and referral status as risk factors for hyperthyroidism.

Risk Factor	Category	Euthyroid n (%)	Hyperthyroid n (%)	Univariable Analysis			Multivariable Analysis		
				OR	95% CI	*P*-value	OR	95% CI	*P*-value
Breed	Domestic shorthair (reference category)	2,625 (77)	786 (23)						
	Burmese (S, CP)	**100 (100)**	**0 (0)**	**0.01**	**0.00–0.26**	**.005**	**0.01**	**0.00–0.23**	**.004**
	Abyssinian (S)	**29 (100)**	**0 (0)**	**0.04**	**0.00–0.76**	**.032**	**0.04**	**0.00–0.74**	**.031**
	Tonkinese (S, CP)	**20 (100)**	**0 (0)**	**0.06**	**0.00–1.06**	**.055**	**0.05**	**0.00–0.95**	**.046**
	Devon Rex (S, cp)	14 (100)	0 (0)	0.08	0.00–1.46	.089	0.08	0.00–1.34	.078
	Persian (L, cp)	**125 (95)**	**7 (5)**	**0.20**	**0.10–0.41**	**< .001**	**0.21**	**0.10–0.44**	**< .001**
	British Shorthair (S, cp)	**109 (94)**	**17 (6)**	**0.53**	**0.32–0.88**	**.015**	**0.47**	**0.28–0.79**	**.004**
	Siamese (S, CP)	**74 (93)**	**6 (7)**	**0.29**	**0.13–0.64**	**.002**	**0.27**	**0.12–0.61**	**.002**
	Birman (L, CP)	26 (93)	2 (7)	0.30	0.08–1.08	.065	0.29	0.08–1.06	.062
	Purebred cross	**58 (92)**	**5 (8)**	**0.31**	**0.13–0.74**	**.008**	**0.32**	**0.13–0.78**	**.012**
	Ragdoll (L, CP)	23 (92)	2 (8)	0.34	0.09–1.22	.097	0.32	0.09–1.17	.084
	Bengal (S, cp)	23 (92)	2 (8)	0.34	0.09–1.22	.097	0.33	0.09–1.21	.095
	Maine Coon (L)	41 (85)	7 (15)	0.59	0.27–1.28	.183	0.56	0.25–1.23	.148
	Oriental (S/L)	13 (81)	3 (19)	0.80	0.25–2.59	.706	0.68	0.21–2.24	.523
	Norwegian Forest (L)	11 (79)	3 (21)	0.93	0.28–3.08	.899	0.82	0.24–2.78	.755
	Domestic Longhair	**335 (72)**	**129 (28)**	**1.29**	**1.04–1.61**	**.021**	**1.31**	**1.05–1.65**	**.017**
Age (years)	10 (reference category)	536 (85)	92 (15)						
	11 to 12	**999 (79)**	**263 (21)**	**1.52**	**1.18–1.97**	**.001**	**1.46**	**1.12–1.90**	**.005**
	13 to 14	**923 (75)**	**302 (25)**	**1.89**	**1.47–2.44**	**< .001**	**1.87**	**1.44–2.43**	**< .001**
	15 to 17	**859 (77)**	**251 (23)**	**1.69**	**1.30–2.19**	**< .001**	**1.90**	**1.46–2.50**	**< .001**
	18 plus	309 (84)	61 (16)	1.14	0.80–1.62	.46	1.36	0.94–1.96	.098
Sex	Male (reference category)	1,955 (81)	445 (19)						
	Female	**1,671 (76)**	**524 (24)**	**1.38**	**1.19–1.59**	**< .001**	**1.40**	**1.21–1.62**	**< .001**
Neuter status	Neutered (reference category)	3,424 (79)	935 (21)						
	Entire	**202 (86)**	**34 (14)**	**0.62**	**0.43–0.90**	**.011**	**0.67**	**0.46–0.99**	**.042**
Referral status	Referral (reference category)	2,199 (73)	795 (27)						
	1st opinion	**1,427 (89)**	**174 (11)**	**0.34**	**0.28–0.40**	**< .001**	**0.31**	**0.26–0.37**	**< .001**

Bayesian logistic regression results for breed, age, sex, neuter status, and referral status as risk factors for hyperthyroidism in cats aged ≥10 years seen at a single UK veterinary teaching hospital between January 2006 and June 2014. Variables with overall $P < .2$ were evaluated in multivariable analyses. Overall *P*-values for risk factors with 3 or more categories, calculated based on the likelihood ratio test, were breed ($P < .001$) and age ($P < .001$). Variables where $P \leq .05$ in the final multivariable model are shown in bold type. Shorthaired purebreds are marked (S), longhaired purebreds are marked (L), purebreds accepted in colorpoint are marked (cp), and breeds fixed for colorpoint are marked (CP).

decreased risk of hyperthyroidism and found evidence for increased risk of disease in longhaired cats. As an epidemiological study, our study establishes associated risk factors but does not establish the mechanism(s) underlying these associations. Regardless of the population-based observations, it remains important that clinicians test for hyperthyroidism in any individual cat where this diagnosis is suspected, regardless of coat color or breed.

It has been proposed previously that the decreased risk of hyperthyroidism noted in certain colorpoint purebreds may be due to mutations in the tyrosinase gene, which may limit utilization of tyrosine for melanin production and potentially result in greater tyrosine availability for thyroid hormone production.[11] We hypothesized that cats with lighter (less pigmented) coat phenotypes, such as colorpoints or those with white markings, would be less likely to be hyperthyroid than cats with darker (more highly pigmented) coat colors. Coat color was not found to have a significant association with risk of hyperthyroidism in nonpurebred cats in our study, and associations between breed and hyperthyroid status could be due to mechanisms unrelated to pigmentation. However, coat color is not always directly related to melanin concentrations. Differences in the base coat colors in cats predominantly result from variation in production of 2 main pigments: brownish-black eumelanin and reddish-yellow pheomelanin. The structure of the final polymer for eumelanin and pheomelanin is unknown, and they may contain similar amounts of tyrosine.[17] This could explain the lack of association between risk of hyperthyroidism and black, red, tabby, and tortoiseshell coat colors in our study. In mice, coat color is related to differences in melanin concentrations in albino, black, and brown fur,[18] but some light-colored phenotypes, such as the dilute trait, result from the optical effects of the distribution of pigment, rather than decreased melanin concentrations.[19] It is therefore possible that some cats with lighter hair coats do not have decreased melanin content.[20]

Our study identified longhaired, nonpurebred cats to be at increased risk of hyperthyroidism compared to shorthaired, nonpurebred cats. This finding is in contrast to previous studies in which differences in the risk of DSH and DLH developing hyperthyroidism either were not found,[8,21] possibly as a result of much smaller sample size, or were not examined.[9] Potential reasons for increased risk of hyperthyroidism in longhaired cats

Table 2. Coat color, hair length, age, sex, neuter status, and referral status as risk factors for hyperthyroidism

Risk Factor	Category	Euthyroid n (%)	Hyperthyroid n (%)	Univariable Analysis			Multivariable Analysis		
				OR	95% CI	*P*-value	OR	95% CI	*P*-value
Color/pattern	Black (reference category)	567 (76)	176 (24)						
	Brown and white	12 (100)	0 (0)	0.09	0.01–1.63	.104			
	Cream	10 (91)	1 (9)	0.41	0.07–2.21	.298			
	Colorpoint	27 (87)	4 (13)	0.51	0.19–1.38	.183			
	White	74 (82)	16 (18)	0.70	0.40–1.23	.219			
	Red	203 (78)	58 (22)	0.92	0.66–1.29	.645			
	Blue	59 (78)	17 (22)	0.93	0.53–1.63	.808			
	Blue and white	48 (77)	14 (23)	0.94	0.51–1.74	.855			
	Black and white	674 (76)	208 (24)	1.00	0.79–1.25	.985			
	Tabby	550 (75)	188 (25)	1.10	0.87–1.40	.404			
	Tabby and white	148 (74)	51 (26)	1.11	0.78–1.59	.557			
	Red and white	109 (74)	38 (26)	1.13	0.75–1.68	.564			
	Tortoiseshell	222 (73)	83 (27)	1.21	0.89–1.63	.220			
	Brown	18 (67)	9 (33)	1.58	0.71–3.51	.262			
	Tortoiseshell and white	48 (67)	24 (33)	1.60	0.96–2.68	.072			
White markings	No white (reference category)	1,656 (75)	539 (25)						
	Some white	1,039 (76)	332 (24)	0.98	0.84–1.15	.821			
	All white	74 (82)	16 (18)	0.67	0.39–1.15	.148			
Dilute	Not dilute (reference category)	1,583 (76)	489 (24)						
	Dilute	117 (79)	32 (21)	0.89	0.59–1.32	.557			
	Unknown	1,069 (74)	366 (26)	1.11	0.95–1.30	.196			
Base pigment	Black (reference category)	1,348 (76)	415 (24)						
	Brown	30 (77)	9 (23)	0.97	0.47–2.04	.949			
	Red	322 (77)	97 (23)	0.98	0.76–1.26	.870			
	Unknown (tabby)	698 (74)	239 (26)	1.11	0.93–1.34	.253			
	Unknown (tortoiseshell)	**270 (72)**	**107 (28)**	**1.29**	**1.00–1.65**	**.047**			
	Unknown (colorpoint)	27 (87)	4 (13)	0.51	0.19–1.38	.183			
	Unknown (white)	74 (82)	16 (18)	0.71	0.41–1.22	.214			
Hair length	Short hair (reference category)	2,459 (76)	764 (23)						
	Long hair	**310 (72)**	**123 (28)**	**1.28**	**1.02–1.60**	**.033**	**1.30**	**1.03–1.64**	**.028**
Age (years)	10 (reference category)	386 (82)	87 (18)						
	11 to 12	**734 (75)**	**246 (25)**	**1.48**	**1.12–1.94**	**.005**	**1.43**	**1.09–1.89**	**.011**
	13 to 14	**716 (72)**	**279 (28)**	**1.72**	**1.31–2.25**	**< .001**	**1.77**	**1.34–2.33**	**< .001**
	15 to 17	**679 (75)**	**223 (25)**	**1.45**	**1.10–1.91**	**.008**	**1.76**	**1.33–2.34**	**< .001**
	18 plus	254 (83)	52 (17)	0.90	0.62–1.32	.599	1.17	0.79–1.72	.436
Sex	Male (reference category)	1,470 (78)	407 (22)						
	Female	**1,299 (73)**	**480 (27)**	**1.33**	**1.15–1.55**	**< .001**	**1.36**	**1.16–1.59**	**.001**
Neuter status	Neutered (reference category)	2,628 (75)	856 (25)						
	Entire	141 (82)	31 (18)	0.68	0.46–1.01	.053			
Referral status	Referral (reference category)	1,611 (69)	732 (31)						
	First opinion	**1,158 (88)**	**155 (12)**	**0.30**	**0.24–0.36**	**< .001**	**0.29**	**0.24–0.35**	**< .001**

Bayesian logistic regression results for coat color/pattern, dilution, base pigment, white markings, hair length, age, sex, neuter status, and referral status as risk factors for hyperthyroidism in nonpurebred cats aged ≥10 years seen at a single UK veterinary teaching hospital between January 2006 and June 2014. Variables with overall $P < .2$ were evaluated in multivariable analysis. Overall *P*-values for risk factors with 3 or more categories, calculated based on the likelihood ratio test, were color/pattern ($P = .129$), white markings ($P = .315$), dilute ($P = .311$), base pigment ($P = .140$), and age ($P < .001$). Variables where $P \leq .05$ in the final multivariable model are shown in bold type.

could include increased requirement for tyrosine for producing pigment. Alternatively, long hair may increase exposure to environmental goitrogens that the cat may ingest while grooming, either by providing a larger overall surface area for exposure, or through more time spent grooming to maintain the long coat. Given that longhaired nonpurebreds were found to be at increased risk of hyperthyroidism, it is possible that hair length also may act as a confounding factor affecting risk of hyperthyroidism in purebreds. Hair length was not examined as a variable in purebreds in our study, because this trait is commonly fixed by breed standards, which causes confounding in statistical analysis. However, in our study, more than one-half (4 of 7) of the GCCF breeds that did not show decreased risk of hyperthyroidism were longhaired breeds, whereas only 1 of the 6 protected breeds (Persian) was longhaired.

Consistent with results from a previous study, our results showed the Burmese breed to be most strongly protected against development of hyperthyroidism.[9] The colorpoint coats of Burmese and Siamese cats occur as a result of 2 separate mutations in the tyrosinase gene, with Burmese cats typically having greater ability to produce pigment in skin covering central body regions than the Siamese.[10] Given that the Siamese polymorphism generally affords greater restriction in pigment production

than the Burmese, Siamese cats might be expected to have relatively greater tyrosine availability resulting in decreased risk of hyperthyroidism compared to Burmese cats, if our hypothesis is correct, but this conclusion was not supported by the results. The Tonkinese breed (which is heterozygous for the Siamese and Burmese tyrosinase polymorphisms) was identified as having decreased risk of hyperthyroidism. However, 2 other breeds fixed for colorpoint coat color, the Birman and Ragdoll, were not found to be significantly protected. Both the Birman and Ragdoll are longhaired breeds, and it is possible that long hair may have acted as a confounding factor if, similar to nonpurebred cats, a longhair coat increases the risk of developing hyperthyroidism.

Aside from potential effects on relative tyrosine availability that may result from pigmentation, the apparent protective effect of breed against development of hyperthyroidism observed in Burmese, Siamese, and Tonkinese cats might be linked to other effects related to the different tyrosinase polymorphisms, or entirely separate genetic or environmental effects. Tyrosinase mutations (and hence colorpoint phenotype) may have an effect on the thyroid gland that is not related to pigmentation (eg, direct effect of enzyme activity, genetic linkage with another trait). The polymorphism in tyrosinase found in Siamese cats is not unique to this breed. It has been found in 50% of Persians and may play a part in the protection observed in this breed and in the Himalayan breed in previous studies.[8,9,22]

Our study identified the Abyssinian and BSH breeds as being at significantly decreased risk of hyperthyroidism. Characteristic features of the coat phenotypes of these breeds might also play a part in their decreased risk of this disease. Polymorphisms in another member of the tyrosinase family, tyrosinase protein I (TYRP1), that result in cinnamon or chocolate coat color are frequent in the Abyssinian breed.[22–24] Mice with TYRP1 mutations have 30–40% less eumelanin in their brown fur than those with wild-type black fur, and if the same is true in cats that segregate for these polymorphisms, this decreased requirement for pigmentation may be associated with decreased risk of hyperthyroidism.[25] British shorthairs are accepted in a range of colors including colorpoint by the GCCF, but this breed is probably most well known for its classic British blue phenotype. The majority of BSH in this study were a dilute color, usually blue, but an effect of color dilution was not found on risk of hyperthyroidism in nonpurebreds. Studies in mice show that dilute hair coat is not always associated with decreased melanin content and this also may be the case in cats.[19,20]

In the univariable analysis investigating the effect of base pigment on risk of hyperthyroidism, tortoiseshell cats were found to be at greater risk of hyperthyroidism when compared to black cats. This effect did not retain significance in the multivariable model and was suspected to be the result of confounding with female sex, due to X chromosome linkage of the tortoiseshell phenotype. In both parts of this study, female cats were found to be at increased risk of hyperthyroidism when compared to males, which is consistent with TNG in people.[26] Although female cats previously have been reported to be at increased risk of hyperthyroidism,[21] the majority of epidemiological studies investigating hyperthyroidism in cats have not found a significant sex effect.[1,8,9,27] The reason for female predisposition to hyperthyroidism is poorly understood, but female sex hormones are suspected to play a role in people.[28,29] Given that neutering of domestic cats is common, it is possible that frequency or timing of neutering in cats may affect the impact of sex-related factors in studies of different populations of cats.

We found intact cats to be at decreased risk of hyperthyroidism compared to neutered cats in the group as a whole, but not in the analysis of nonpurebreds only. Our results with regard to neuter status may be unreliable, because being recorded as intact is a default setting on our hospital's EPRs and, as such, cats with unknown or unrecorded neuter status are more likely to have been recorded as intact. Arguably, this may be more likely to occur in emergency cases and less likely in cats referred for medical procedures such as radioactive iodine treatment.

Increased age previously has been found to be a risk factor in several studies of hyperthyroidism in cats. In our study, cats ≥18 years of age were not at increased risk compared to cats aged 10 years. This observation may indicate that peak incidence of hyperthyroidism occurs before this age or may be a result of decreased longevity in hyperthyroid cats, or a decreased tendency to refer very old cats for radioactive iodine treatment. Ages were similar among breed groups in our study (data not shown), and age was included as a confounder in the logistic regression analyses to adjust for potential effects of age differences in breed groups.

Our study was conducted using data from a referral hospital, and the high prevalence of hyperthyroidism most likely was attributable to referral of hyperthyroid cats to this center specifically for radioactive iodine treatment and is not suggested to be reflective of the UK population as a whole.[9,27] The study population also included patients that had been seen as emergency first-opinion cases out of hours, where access to the previous medical history may have been limited and in some cases may have resulted in the status of cats being incorrectly reported as euthyroid. Although, as expected, more referral than first-opinion patients were hyperthyroid, rerunning the analysis excluding all of the first-opinion patients did not significantly alter the results of the analysis (data not shown). As such, it is unlikely that potential differences in demographics (particularly regarding breed) of the first-opinion and referral populations acted as a confounder in the analysis for risk of hyperthyroidism. Additionally, other diseases can be prevalent in some purebreds which could lead to an apparently less frequent diagnosis of hyperthyroidism in a hospital population, if certain breeds were more likely to be referred to other services at our facility.

Overall, the results of our study do not provide consistent evidence in support of the proposed hypothesis for an association between coat color and hyperthyroid status. However, the study was based on the assumptions that coat color is reflective of melanin

concentration and that degree of pigmentation affects relative tyrosine availability for thyroid hormone production and was subject to certain limitations. The genetics of coat color are complex, and cats could have been misclassified because of the use of owner-reported or receptionist-recorded information. Differences in the terminology used for coat colors by breeders and geneticists and lay terminology might also have compounded this effect. Additionally, hyperthyroidism is suspected to be a multifactorial disease, and data regarding other known risk factors for hyperthyroidism, such as diet, were unavailable and could not be included in the analysis.

In summary, our results indicate that certain breeds have decreased risk of hyperthyroidism and that long-haired cats are at increased risk of hyperthyroidism. Further research is necessary to determine whether pigmentation plays a role in this breed protective effect or whether this association is as a result of alternative mechanisms.

Footnote

[a] R i386 version 3.2.2, R Foundation for Statistical Computing, Vienna, Austria

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Conflict of Interest Declaration: Authors declare no conflict of interest.

Off-label Antimicrobial Declaration: Authors declare no off-label use of antimicrobials.

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