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Prevalence of Hypertrophic Cardiomyopathy in a Cohort of British Shorthair Cats in Denmark

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Background: Familial hypertrophic cardiomyopathy (HCM) has been described previously in British Shorthair cats (BSH), but until now, no reports have been published describing the prevalence of the disease within this breed.

Objectives: The aim of this study was to assess the prevalence of HCM in a large cohort of BSH and to evaluate the effect of sex, weight, and increasing age as potential risk factors for this disease.

Animals: Three hundred and twenty-nine BSH presented for routine HCM screening during a 4-year period.

Methods: Prospective cross-sectional study in which all cats were screened for HCM by conventional echocardiography.

Results: A total of 329 cats were examined, 214 females and 115 males, with a median age of 2.3 years (range, 0.8–14.1). Twenty-eight cats (8.5%) were classified as HCM-positive, 14 (4.3%) as equivocal, 282 (85.7%) as HCM-negative, and 5 (2.1%) were diagnosed with other cardiac diseases. The median age for diagnosis of HCM was 2.7 years (range, 0.9–14.1). Male cats had a significantly higher occurrence of HCM (20.4%) compared with the females (2.1%) corresponding to an odds ratio of 7.89 (95 % CI, 2.54–28.08) for males versus females adjusted for age and weight ($P < .001$).

Conclusion: The BSH in our cohort had a high prevalence of HCM, often of early onset and with a significant male sex predisposition. We strongly recommend echocardiographic screening in this breed, especially cats used for breeding.

Key words: Feline; HCM; Screening; TDI.

Hypertrophic cardiomyopathy (HCM) is the most commonly diagnosed heart disease in cats.[1,2] Primary HCM is characterized by left ventricular concentric hypertrophy (LVH) and diastolic dysfunction in the absence of other cardiac or systemic disorders that may cause LVH.[3,4] Echocardiography is the gold standard for diagnosing HCM, for which a wide morphologic spectrum of hypertrophic changes and functional impairment can be observed. The myocardial changes can be generalized and substantial or asymmetric, predominately affecting either the interventricular septum (IVS) or left ventricular free wall (LVFW).[5,6] More focal forms of HCM also have been described in which segments such as the papillary muscles or basal septum are regionally hypertrophied.[3,5,6] Other echocardiographic findings associated with HCM include systolic anterior motion of the mitral valve (SAM), end-systolic cavity obliteration, enlargement of the left atrium (LA), and diastolic dysfunction, most commonly detected by pulsed wave Doppler imaging of mitral inflow (MI) and diastolic velocity profiles of the mitral annulus by tissue Doppler imaging (TDI).[3,7–9] HCM has been diagnosed in cats of all ages, ranging from 3 months to 18 years, with an average age at diagnosis of approximately 6 years.[3,10,11] Male cats generally are considered predisposed to earlier and more aggressive development of the disease[10,11] and it also has been hypothesized that cats of large stature are at increased risk.[12]

Abbreviations:

a'	maximal late diastolic myocardial velocity
Ao	aorta
BSH	British Shorthair cats
e'	maximal early diastolic myocardial velocity
HCM	hypertrophic cardiomyopathy
LV	left ventricle
LVH	left ventricular hypertrophy
LA	left atrium
MI	mitral inflow
OR	odds ratio
SAM	systolic anterior motion of the septal leaflet in the mitral valve
TDI	tissue Doppler imaging
2D	2-dimensional

In the Maine Coon and Ragdoll, dominant patterns of inheritance have been documented, and 2 separate mutations in the cardiac myosin binding protein C gene (cMYBPC3) have been associated with development of HCM in these 2 breeds.[6,13,14] Although familial occurrence, indicative of a genetic underlying cause, has been reported in several other breeds considered predisposed to development of HCM such as in British Shorthair (BSH),[a] Persian,[b] and American Shorthair[c] cats, no relevant HCM-associated mutations have yet been identified. In several HCM-affected breeds there has been increased interest in screening cats before breeding to decrease the incidence of the disease, and in the absence of genetic tests in most affected breeds, echocardiography remains the most informative and feasible primary screening tool.

Although HCM is regarded as a very common cardiac disease in cats, few studies are available that estimate the prevalence in the general cat population of Domestic Shorthairs[15] and in breeds considered predisposed.[16–18]

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Information regarding prevalence of HCM in different breeds has clinical relevance because it has a bearing on the potential value of echocardiographic screening and direction of future genetic research. The aim of this study was to investigate the prevalence of HCM in a large cohort of BSH in Denmark. Additionally, we wanted to investigate the association between selected potential risk factors (sex, age, and weight) and the disease.

Materials and Methods

Study Population

The study was conducted as a cross-sectional study at the Department of Small Animal Clinical Sciences, Faculty of Life Sciences, University of Copenhagen, where all BSH cats presented for HCM screening during a 4-year period (2006–2009) were prospectively included. Owner consent was given before enrolment and the study was approved by the ethical committee at the Department. Cats had to be >10 months old and eligible for examination without sedation in order to participate. A routine clinical examination of the cardiovascular system was performed in all animals. Cardiac murmurs detected by auscultation were graded on a scale of I–VI and the PMI was determined.[19] Body weight, sex, pregnancy, or lactation status and whether or not the cat was neutered also was recorded. In addition, the owners were asked about known familial occurrences of HCM.

Echocardiographic Examination

All cats were examined by the same 2 trained ultrasonographers by a Vivid 7 ultrasonographic system[d] with a 10S multifrequency phased array transducer (4–11.5 MHz). The cats were manually restrained and examined from below in lateral recumbency over a cut-out in the examination table.[20] All echocardiographic examinations were digitally stored and data for this study were analyzed by 1 observer by specialized software.[e]

Cats were classified as HCM-positive, HCM-negative, equivocal, or diagnosed with other cardiac disease based on a screening protocol of the LV in right parasternal long-axis and short-axis views. The examination included standard 2-dimensional (2D), M-mode, and color flow Doppler imaging according to recommendations.[21] In all HCM-positive and equivocal cats, spectral Doppler examination of MI, aortic outflow, and TDI of the IVS and LVFW also were performed.

Conventional Echocardiography and Screening Classification

Standardized measurements of left ventricular wall thickness and chamber dimensions were obtained from a 2D guided M-mode examination at the level of the chordae tendinae in a right parasternal short-axis view by the leading-edge to leading-edge methodology.[22] Additionally, maximum diastolic wall thickness was evaluated from 2D short-axis and long-axis views according to a segmental approach previously described by Fox et al[3] and if the diastolic wall thickness exceeded 5.5 mm, the highest value from the 2D segmental approach was reported. A 2D right parasternal short-axis view of the heart base was used to evaluate LA- and aortic (Ao) diameters,[23] and LA enlargement was considered to be present if the LA/Ao ratio was >1.5. Cats with turbulent blood flow in the left ventricular outflow tract detected by color flow Doppler were evaluated for SAM by 2D and M-mode imaging of the septal leaflet in a right parasternal long-axis view. Presence of end-systolic obliteration and papillary muscle size were subjectively evaluated from the short axis view at level of the papillary muscles. Cats were classified as HCM-positive if the maximum diastolic wall thickness obtained by the 2D examination exceeded 5.5 mm in >50% of segment length as evaluated from short-axis and long-axis views, or if the papillary muscles were severely hypertrophied in cats with normal wall thickness.[24–26] The hypertrophic changes were considered to be asymmetric if the ratio of maximum diastolic wall thickness of the IVS/LVFW was >1.3 or ≤0.7.[18] Cats were categorized as equivocal if they had a normal wall thickness but displayed moderate papillary muscle hypertrophy, SAM, or both.

TDI and Spectral Doppler Examinations

Maximal systolic velocity of aortic flow and early (E) and late (A) diastolic velocities of MI were determined by use of continuous wave and pulsed-wave Doppler in the apical 5-chamber and 4-chamber view, respectively. Image acquisition for longitudinal myocardial diastolic velocity profiles by 2D color TDI was performed in a standard left apical 4-chamber view with continuous ECG monitoring. The sector image was narrowed for wall-by-wall acquisition to optimize myocardial alignment and increase the frame rate. Color TDI was superimposed on the 2D image at a frame rate of >300 frames/s and the Doppler velocity range was set at the minimum value at which no aliasing occurred. Sampling was performed in the basal IVS and LVFW wall using a 3×1 mm region of interest that was tracked through the cardiac cycle by a semiautomatic tracking system. Parameters obtained for evaluation included peak early (e') and late (a') diastolic velocity, the e'/a' ratio and the E/e' ratio calculated as an average of IVS and LVFW values. All velocity variables were calculated as an average of measurements from 3 consecutive heartbeats.

Exclusion of Differential Diagnoses

Blood pressure was measured according to a previously described indirect oscillometric method[27] in all cats classified as HCM-positive based on the echocardiographic examination. Baseline systolic pressure was calculated as an average of 5 measurements and had to be <160 mmHg for the cat to be included in the study.[28] Routine serum biochemistry, hematology, and total thyroxine (T_4) concentration also were analyzed. Cats with azotemia (reference creatinine concentration 60–170 μmol/L) and a T_4 >35 nmol/L were excluded from the study.

Statistical Analyses

All continuous data were tested for normality by a Shapiro-Wilk *W*-test, and normally distributed variables are presented as mean ± standard deviation (TDI and spectral flow-Doppler variables), skewed variables as medians and range (age, weight, and conventional echocardiographic parameters), and categorical data as number and proportions. Continuous variables were compared among the HCM-negative, equivocal and HCM-positive groups by means of the Kruskal-Wallis test and the post hoc pairwise comparisons between groups were subjected to Bonferroni's adjustment. Proportions of dichotomous variables were compared by Fischer's exact test. A logistic regression model was used to capture the effect of sex, age, and weight on HCM status. Because of the presence of the equivocal group, this was performed in 3 different ways: (i) excluding the equivocal cats, (ii) merging them with the HCM-negative group, and (iii) merging them with the HCM-positive group. Model reduction was done by backwards elimination with a 5% cut-off level, and odds ratio (OR) estimates are provided with 95% confidence limits that were calculated on a log-scale and back-transformed. All analyses were performed by SAS software[f] and *P*-values < .05 were considered statistically significant.

Results

Animals

The study group comprised 329 cats; 65.0% (n = 214) of these were females and 35% (n = 115) males. Eighteen

(15.7%) of the males and 15 (7.0%) of the females were neutered and 6 (2.8%) of the females were pregnant or lactating at the time of examination. The median age of the cohort at examination was 2.3 years (range, 0.8–14.1) and the median weight was 4.2 kg (range, 2.2–8.3).

Physical Examination

Thirty-eight cats (11.6%) had auscultatory abnormalities characterized by systolic murmurs (36) and gallop sounds without murmurs (2). Twenty-seven of these 38 cats were classified as HCM-positive, 5 as equivocal, 4 were diagnosed with other cardiac disease, and in 2 cats no cardiac abnormalities could be detected. Only 1 of the HCM affected cats was normal on auscultation. One cat presented with tachypnea and was diagnosed with congestive heart failure because of HCM, but all other cats were asymptomatic.

Prevalence of HCM

Twenty-eight cats (8.5%) were classified as HCM-positive, 14 (4.3%) as equivocal, 282 (85.7%) as HCM-negative, and 5 cats (1.5%) were diagnosed with other cardiac diseases. The HCM-positive group had a significantly higher proportion of male cats ($P < .001$) (Fig 1) and a higher average weight ($P < .001$) compared with the 2 other groups, whereas the equivocal group was significantly older than the others ($P < .001$) (Table 1).

Among the 28 HCM-positive cats, 82.1% (n = 23) were males, corresponding to a HCM prevalence of 20.0% (23/115) among the males and 2.3% (5/214) among the females. The median age at diagnosis in both sexes was 2.7 years (range, 1.1–14.1 for males; range, 0.9–4.1 for females).

Seventeen of the affected cats, (60.7%) had a familial history of HCM in which parents, littermates, or several offspring had a verified diagnosis. Thirteen of these cases involved a parental history of HCM, and for all of them, only 1 parent was known to suffer from the disease. Sire to offspring inheritance was the most common finding.

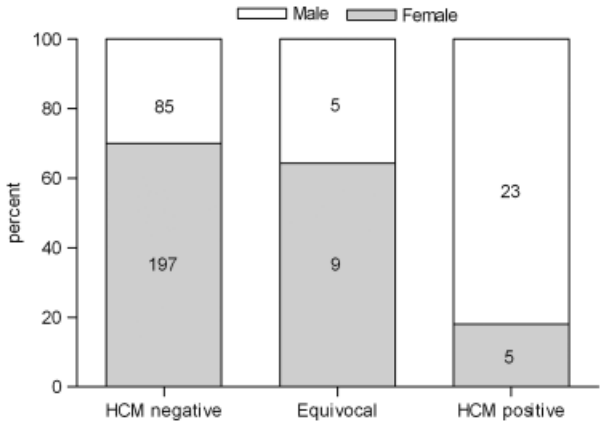

Fig 1. Sex distribution among healthy (n = 282), equivocal (n = 14), and HCM-positive cats (n = 28). HCM, hypertrophic cardiomyopathy.

Additional Echocardiographic Characterization of HCM-Positive Cats

Symmetric hypertrophy affecting the entire LV was the most common finding, present in 78.6% of the 28 HCM-positive cats (n = 22). Four of the cats had asymmetric hypertrophic changes affecting most of either the IVS or LVFW and 2 cats had regional hypertrophy in the anterior or basal septum. Because of the patterns of hypertrophy, the M-mode examination was able to identify all affected cats. Twenty-three (82.1%) of the cats had SAM, 25 (89.3%) end systolic cavity obliteration, 24 (85.7%) subjectively enlarged papillary muscles (Table 1), and 2 (7.1%) LA enlargement. The average velocity of aortic flow in the HCM-positive group was 3.6 ± 1.3 m/s for cats with SAM and 1.0 ± 0.1 m/s for cats without SAM.

Temporal resolution of early and late diastolic events could be obtained in 53.6% (n = 15) for MI and an E/A ratio of <1 was found in 11 of these individuals. Myocardial diastolic velocity profiles with splitting of e' and a' could be obtained in 60.7% of the cats (n = 17) in the IVS and in 57.1% (n = 16) in the LVFW. Evidence of diastolic dysfunction defined by an e'/a' ratio <1 was found in all 17 cats in the IVS and in 10 cats in the LVFW (Table 2). The E/e' ratio was found to be 14 ± 3 in HCM-affected cats.

Of the cats classified as HCM-positive, 21.4% (n = 6) had a myocardial thickness between 5.5 and 6.0 mm. All of these individuals had at least 2 or more additional echocardiographic sign in agreement with the diagnosis (4/6 papillary muscle hypertrophy, 4/6 SAM, 6/6 obliteration). Additionally, diastolic dysfunction was confirmed by MI and TDI in 3/3 of these cats where the heart rate was low enough to allow measurements of diastolic events.

Risk Factors for Development of HCM

Logistic regression with sex, age, and weight as potential risk factors for HCM indicated that only sex significantly affected the odds of HCM if the equivocal group was excluded or merged with the HCM-negative group. In these analyses, the OR for sex adjusted for age and weight were found to be 7.89 (95% CI, 2.54–28.08) and 7.81 (95% CI, 2.53–27.61), respectively. If the equivocal group was merged with the HCM-positive, then both sex and age were significant factors, with an age and weight adjusted OR for sex of 3.66 (95% CI, 1.52–9.01) and a sex and weight adjusted OR per year increase in age of 1.14 (95% CI, 0.99–1.31).

Discussion

In this study we found a high prevalence of HCM (8.5 %) in our cohort of BSH with a clear male sex predisposition. The median age at diagnosis was 2.7 years, and we found HCM-positive cats as young as 10 months of age, showing that BSH can have HCM of early onset, similar to what has been documented for the Maine Coon[6] and Ragdoll.[g] Although the median age at diagnosis was the same for both male and female cats, the large difference in prevalence between the sexes could indicate that female BSH generally develop HCM later in life.

Table 1. Overview and comparison of clinical and selected echocardiographic variables between the HCM-positive, equivocal, and HCM-negative groups.

Variable	HCM-Negative (n = 282)		Equivocal (n = 14)		HCM-Positive (n = 28)		*P*-Value
Baseline parameters							
Age (years)	2.1	(0.8–13.3)	4.2*	(0.9–11.3)	2.7	(0.9–14.1)	.006
Weight (kg)	4.1	(2.2–8.3)	4.6	(3.5–7.2)	5.2**	(3.5–7.5)	<.001
Echocardiographic variables							
Interventricular septum diastole (mm)	3.8*	(2.6–5.2)	5.1*	(4.3–5.5)	6.9*	(5.1–9.2)	<.001
Left ventricular free wall diastole (mm)	3.8*	(2.6–5.0)	4.6*	(3.1–5.5)	6.7*	(3.7–14.4)	<.001
Left ventricular diameter diastole (mm)	15.0	(11.0–21.2)	13.8**	(11.5–18.4)	13.9**	(10.0–14.2)	.011
Left ventricular diameter systole (mm)	7.4	(0.5–12.1)	5.8**	(2.2–8.5)	5.8**	(0–8.9)	<.001
Fractional shortening (%)	50	(29–95.8)	58**	(41–84)	60**	(31–100)	<.001
Aortic diameter (mm)	8.7	(6.1–11.5)	8.9	(6.7–12.0)	9.2**	(6.4–11.7)	.015
Left atrial diameter (mm)	9.5	(6.7–14.4)	10.1	(7.3–14.2)	12.5*	(7.8–37.4)	<.001
Left atrium/aorta	1.1	(0.9–1.4)	1.1	(0.9–1.3)	1.4*	(0.9–4.6)	<.001
Subjectively enlarged papillary muscles (%)	1.4		85.7**		85.7**		<.001
Occurrence of obliteration (%)	7.8*		64.3*		89.3*		<.001
Systolic anterior motion (%)	0*		7.1*		82.1*		<.001

Continuous variables are expressed as medians with ranges and proportions are expressed as percentages.
HCM, hypertrophic cardiomyopathy.
*Significant difference compared with both other groups.
**Significant difference compared with the HCM-negative cats.

This is, to the author's knowledge, the largest prevalence investigation performed in one of the breeds considered predisposed to HCM. Similar prevalence studies in screening populations have been conducted in the Maine Coon (9.5–15%)[17,18,26] and a screening cohort consisting of 5 different breeds of cats (8.3%).[16] Our estimated occurrence is similar to those found in these reports, although different methods of patient recruitment and diagnostic criteria have been used. Concentric hypertrophy in agreement with HCM is in most other studies defined as a diastolic wall thickness >6 mm in >50% of the LV wall.[3,15] However, a cut-off value of 5.5 mm[24] and separate values for the IVS and LVFW of 6.0 and 5.5 mm[9] also have been recommended. Recently, it has been suggested that the wall thickness of a normal cat in most cases is <5.0 mm, and that individuals with measurements above this value could be considered to be affected.[17] In this study, a decision limit of 5.5 mm was chosen and approximately 20% of our affected cats had a wall thickness between 5.5 and 6.0 mm. However, in all of these cats at least 2 additional echocardiographic changes associated with HCM were detected, strengthening the classification of these individuals.

Table 2. Longitudinal diastolic velocity parameters by color tissue Doppler imaging in the equivocal and HCM-positive group.

Variable	Equivocal (n = 14)	HCM-Positive (n = 28)
Longitudinal diastolic myocardial velocities IVS	n = 7	n = 17
e' basal IVS (cm/s)	3.8 ± 1.6	3.7 ± 1.1
a' basal IVS (cm/s)	4.2 ± 1.1	5.1 ± 1.4
e'/a' ratio basal IVS	0.9 ± 0.3	0.7 ± 0.2.
Proportion of cats with e'/a' < 1 IVS	5/7	17/17
Longitudinal diastolic myocardial velocities LVFW	n = 8	n = 16
e' basal LVFW (cm/s)	3.8 ± 1.4	4.3 ± 1.5
a' basal LVFW (cm/s)	3.5 ± 1.2	4,2 ± 1.4
e'/a' ratio basal LVFW	1.2 ± 0.4	1.1 ± 0.4
Proportion of cats with e'/a' <1 LVFW	4/8	10/16

Data are expressed as mean ± standard deviation.
HCM, hypertrophic cardiomyopathy; IVS, interventricular septum; LVFW, left ventricular free wall; e' and a', longitudinal myocardial velocities during early and late diastole, respectively; N, number of animals included for each method of analysis, because temporal resolution of diastolic events could not be obtained in all cats.

During screening it is difficult to completely avoid equivocal outcomes, and the classification is often based on criteria such as papillary muscle size. The typical equivocal cat in this study was an individual in the upper range of normal myocardial wall thickness, displaying mild, or moderate hypertrophy of papillary muscles and obliteration. TDI and PW-Doppler of MI indicated diastolic dysfunction in some of these individuals, but follow-up examinations will be necessary to determine whether more definite echocardiographic signs of HCM will develop. Because the equivocal group was significantly older than the rest of the cohort and increasing age is associated with diastolic dysfunction,[29] some of the observed mild myocardial changes may be secondary to aging and extracardiac conditions more commonly encountered in the older cat.

The pattern of hypertrophy in HCM-affected cats has primarily been described in study populations dominated by Domestic Shorthairs, where generalized hypertrophy of the LV as seen in our cohort has been the most common finding in 2 of 3 studies (range, 41–67%).[3,5,25] However, in Maine Coon cats, the LVFW is more commonly affected than the rest of the LV,[6] illustrating that different breeds may very well be predisposed to different patterns of hypertrophy.

In our cohort, cardiac auscultation had a high sensitivity in detecting HCM because only one of the affected cats was normal on auscultation. This is a higher prevalence of cardiac murmurs in HCM-affected cats than previously reported[10,15,17,25,26] and could be explained by the high occurrence of symmetric hypertrophic changes, obliteration, and SAM among affected BSH, because all of these findings are associated with murmurs.[25] Although we consider auscultation a valuable tool during HCM screening in breeding animals, with the results of other studies taken into consideration, we would not recommend to use only auscultation for screening purposes, as the risk of missing especially early stages of the disease could potentially be high.

In the HCM risk analysis, male sex was the only factor that was consistently associated with a HCM-positive status. This male predisposition is in agreement with several other studies[10,11] and indicates that female BSH may have HCM of later onset or with more subtle myocardial changes. Increasing age was an additional significant risk factor if the equivocal group was merged with the HCM-positive group. However, the diagnostic uncertainty in the former group imposes difficulties in drawing any major conclusions from this result. The fact that weight was not a significant risk factor shows that although the HCM-positive group was significantly heavier compared with the others, this finding can be attributed to the high proportion of male cats within the group. Unfortunately, a risk analysis involving familial history of HCM could not be performed because of insufficient data in a majority of the cats. However, it is noteworthy that approximately half of the affected cats had 1 HCM-positive parent, and that several cases of sire and male offspring cases were noted, excluding an X-linked pattern of inheritance.

Our reported prevalence may represent an underestimation of the overall occurrence in the breed, because of the skewed sex distribution. Our results indicated a strong male sex predisposition, and yet males constituted a smaller proportion of screened cats. Moreover, approximately 3% of the female cats were lactating or pregnant at time of examination, which could potentially affect LV performance and mask mild myocardial hypertrophic changes because of the natural volume overload state associated with both conditions. In addition to this, we had an equivocal group and a high proportion of young cats that may develop HCM in the future. On the other hand, breeders with known cases of HCM in their lines may be more prone to screen for the disease, which could lead to an overestimation of occurrence. One additional important factor to be considered is that the genetic relatedness of cats in a small country such as Denmark most likely will be higher than in a larger country with a larger gene pool. Therefore, if there indeed is an underlying genetic cause of HCM in the breed, this could strongly affect the estimated prevalence. Even with the previously discussed epidemiological reservations, we believe that the prevalence of HCM in our cohort may provide a reasonable estimate of the frequency of HCM within the breed. Based on our results, we strongly recommend echocardiographic screening in BSH, especially in cats used for breeding or with a family history of heart disease.

Footnotes

[a] Putcuyps I, Coopman F, Vad De Werf G. Inherited hypertrophic cardiomyopathy in British Shorthair cats. J Vet Intern Med 2003;17:439 (abstract)

[b] Martin L, VandeWoide S, Boon J, Brown D. Left ventricular hypertrophy in a closed colony of Persian cats. J Vet Intern Med 1994;8:143 (abstract)

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[d] Vivid 7, GE Healthcare, Brøndby, Denmark

[e] EchoPac for PC, 7.0, GE Healthcare

[f] SAS, 9.1 for PC, Cary, NC

[g] Lefbom BK, Rosenthal SL, Tyrrell Jr WD, Saunders TG, Ferguson MJ, Rusj JE. Severe hypertrophic cardiomyopathy in 10 young Ragdoll cats. J Vet Intern Med. 2001;15:308 (abstract)

Acknowledgment

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