



Prevalence of the MYBPC3-A31P mutation in a large European feline population and association with hypertrophic cardiomyopathy in the Maine Coon breed

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Abstract Objectives: The MYBPC3-A31P mutation has been identified in the USA in a colony of Maine Coon cats with an autosomal dominant hypertrophic cardiomyopathy (HCM). The objectives of this prospective study were: 1) to evaluate the prevalence of this mutation in a large feline population from Europe; 2) to compare these data with the prevalence of HCM in the Maine Coon breed.

Animals and methods: 1) 3757 cats from different breeds including 2744 Maine Coon cats were screened for the mutation. 2) 164/2744 Maine Coon cats were subjected to echocardiography (Echo-Group, mean age = 2.6 years [0.3–11.5]).

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Results: 1) In the whole study population, the mutation was only found in Maine Coon cats (prevalence = 41.5%), except for one British Longhair cat. 2) 55/164 (34%) cats from the Echo-Group carried the mutation while only 12/164 (7%; 5/48 heterozygous, 5/7 homozygous mutated, 2/109 homozygous wild-type cats) showed HCM. MYBPC3-A31P was associated with a significant increased risk of HCM (relative risk = 9.91).

Conclusion: The MYBPC3-A31P mutation is highly prevalent in Maine Coon cats in Europe and appears to be breed specific with potential marginal events. Young unaffected mutated cats and affected homozygous wild-type cats illustrate the phenotypic and etiological heterogeneity of feline HCM, as demonstrated in humans. © 2010 Elsevier B.V. All rights reserved.

Introduction

Hypertrophic cardiomyopathy (HCM) is a myocardial disorder characterized by concentric hypertrophy of the left ventricle (LV) in the absence of an obvious cause such as systemic arterial hypertension or hyperthyroidism.^{1–3} Hypertrophic cardiomyopathy is one of the most common cardiovascular diseases in humans affecting about 1/500 people, and is considered as familial in at least 60% of cases with an autosomal dominant trait.^{4,5} More than 455 independent causative mutations in 22 myofibril-related genes have been identified up to now (<http://www.cardiogenomics.org> and OMIM, Online Mendelian Inheritance in Man, <http://www.ncbi.nlm.nih.gov/omim> #192600).^{6–8} Several of these mutated genes encode sarcomeric proteins including the alpha and beta myosin heavy chains, cardiac troponins T, I and C, alpha tropomyosin, actin, titin and cardiac myosin binding protein C (MYBPC3).^{6,9}

Hypertrophic cardiomyopathy has been described in several animal species, particularly in cats and dogs.^{10,11} Hypertrophic cardiomyopathy is the most common feline heart disease and is also a major cause of morbidity and mortality associated with a high risk of sudden death, congestive heart failure, and aortic thromboembolism in this species.^{1,2,12} Feline HCM is currently diagnosed by two-dimensional (2D) and M-mode echocardiography demonstrating a variety of global or regional hypertrophic patterns, predominantly involving the interventricular septum (IVS) and the left ventricular free wall (LVFW).

In 1999, HCM was described in a family of American Maine Coon cats as an inherited disorder with evidence of an autosomal dominant mode of inheritance and complete penetrance.¹³ In 2005, one causative mutation was identified in the MYBPC3 gene for inherited HCM in a Maine Coon colony.¹⁴ The mutation was shown to be a guanine-to-cytosine transition in MYBPC3 exon 3 (G93C),

inducing the production of an aberrant protein by changing the conserved alanine of the 31st codon into a proline (A31P).¹⁴

A prospective study was recently undertaken on a worldwide panel of cats (non-diagnosed for HCM), and the prevalence of the G93C mutation was shown to be high in the Maine Coon breed (34%).¹⁵ However, the exact prevalence of the mutation in European cats is still unknown. Moreover, few data are available regarding the prevalence of HCM in the Maine Coon breed and its association with the genetic status.^{16,17}

The aims of this prospective study were therefore: 1) to investigate the prevalence of the MYBPC3 mutation and its breed specificity in a large European cohort of various feline breeds, 2) to assess the prevalence of HCM in a population of European Maine Coon cats using conventional echocardiography, and 3) to associate the HCM phenotype with the mutation in MYBPC3 in a phenotyped sub-population.

Animals, material and methods

Animals

Cats from various breeds with or without a known phenotypic status (i.e., with or without prior echocardiographic examination) were screened for the Maine Coon cat MYBPC3 mutation by the Antagene laboratory (JM, AT) using buccal swab kits, between 2006 and 2009. Owner's consent was obtained for each cat before its inclusion in the study. Samples were provided by both European breeders and various European veterinary clinics.

A group of Maine Coon cats (Echo-Group) was distinguished within this study population. Maine Coon cats examined in a single cardiology department (Cardiology Unit of Alfort) between 2006 and 2009 for which the owner's consent was obtained for both DNA analysis (MYBPC3-A31P mutation) and

echocardiographic examination were included in this Echo-Group. All cats from the Echo-Group underwent echocardiography by a trained observer (CCS, VC, VG).¹⁶ Only one imaging center was utilized in order to limit the bias in echocardiographic measurements induced by inter-observer variability.¹⁸ Pathological hypertrophy was defined as a diastolic LVFW or IVS thickness ≥ 6 mm using 2D or M-mode echocardiography.^{1–3} In cats >4 years old with an LV hypertrophic pattern, HCM was diagnosed after excluding both systemic arterial hypertension (systolic arterial blood pressure <160 mmHg in unstressed cats) and hyperthyroidism (total thyroxin plasma levels [T4], reference interval: 10–50 nmol/L).¹⁹

Mutation analysis

DNA extraction

Genomic DNA was extracted from buccal swab samples preserved in ethanol using the NucleoSpin[®] 96 Tissue DNA Kit according to the manufacturer's instructions.^f

Mutation testing

Cats were screened for the G93C mutation identified in *MYBPC3*.¹⁴ Polymerase chain reactions using especially designed primers were processed from 20 ng genomic DNA amplified with the Eurobluetaq[®] DNA polymerase.^g The PCR products were sequenced using the BigDye[®] Terminator v 3.1 Cycle Sequencing Kit and run on an Applied Biosystems 3100 sequencer.^h

Classification used in this study

Maine Coon cats were regarded as wild-type when they were homozygous at the *MYBPC3* locus (G/G), homozygous mutated when they carried 2 copies of the mutated allele (C/C), and heterozygous when they carried one copy of the mutated allele (G/C). The designation "mutated cats" will be used to bring together the heterozygous and homozygous mutated Maine Coon cats. Lastly, Maine Coon cats with HCM will be considered as "affected cats".

Statistical analysis

Data are expressed as mean \pm SD. Ages were compared between groups using a one-way ANOVA followed if necessary by a Fisher's Protected LSD.ⁱ

Proportions were compared between groups using a chi-square test. Relative risk (RR) of developing HCM was calculated in mutated versus homozygous wild-type cats. This calculation was performed conventionally (i.e., without modelling), assuming that this is a ratio of the proportion of an event occurring in an exposed group versus a non-exposed group. CI 95% was defined as RR/EF to RR \times EF (CI 95%: confidence interval, EF: error factor). EF was calculated using the standard error (s.e.) of the log(RR): EF = exp(1.96 \times s.e. log(RR)). *P* values <0.05 were considered as statistically significant.

Results

Prevalence and breed specificity of the MYBPC3-A31P mutation in the whole study population (*n* = 3757)

A total of 3757 cats from 11 different countries and from 17 different breeds were screened for the mutation (Table 1). Samples came mostly from France, but also from Belgium, Denmark, Germany, Italy, Liechtenstein, Luxemburg, the Netherlands, Poland, Spain and Switzerland. The most represented breed was Maine Coon (*n* = 2744), including 58.5% wild-type cats (1605/2744), 38.0% heterozygous cats (1044/2744) and 3.5% homozygous mutated cats (95/2744). The prevalence of the mutation in the Maine Coon breed was therefore 41.5% (1139/2744). All cats of other breeds (*n* = 1013) mostly represented by Persian (685/1013; 67.6%) and Exotic Shorthair cats (137/1013; 13.5%), were negative for the MYBPC3-A31P mutation, with the exception of one of the two British Longhair cats that was heterozygous for the mutation.

Prevalence of the HCM phenotype in the Echo-Group (*n* = 164); association with the genotype

The Echo-Group included 164 Maine Coon cats. The genotyping and phenotyping data are compared in Table 2. Of these 164 Maine Coon cats, 66% cats were wild-type (109/164), 30% were heterozygous (48/164), and 4% were homozygous mutated (7/164). The overall prevalence of the mutation was therefore 34% (55/164).

The prevalence of HCM in the Echo-Group was 7% (12/164, Table 2) and was significantly different from that of the mutation ($P \leq 0.0001$). Hypertrophic cardiomyopathy was diagnosed in both wild-type and mutated cats. The penetrance was 18% at 2.6 ± 2.0 years old. In the sub-population of

^f NucleoSpin 96 Tissue DNA kit, Macherey–Nagel, Hoerd, France.

^g Eurobio, Courtaboeuf, France.

^h Applied Biosystems, Foster City, CA.

ⁱ Systat, version12, SPSS Inc, Chicago, Ill.

Table 1 Presentation of the whole study population including 3757 cats from 11 European countries screened for the MYBPC3-A31P mutation.

Breed	N	Genotype			% carriers ^a
		G/G	G/C	C/C	
Maine Coon	2744	1605	1044	95	41.5
Bengal	1	1	0	0	0.0
Birman	26	26	0	0	0.0
British Longhair	2	1	1	0	50.0
British Shorthair	43	43	0	0	0.0
Burmese	1	1	0	0	0.0
Chartreux	5	5	0	0	0.0
Devon Rex	4	4	0	0	0.0
European Shorthair	10	10	0	0	0.0
Exotic Shorthair	137	137	0	0	0.0
Norwegian	7	7	0	0	0.0
Forest Cat					
Ocicat	1	1	0	0	0.0
Persian	685	685	0	0	0.0
Pixie Bob	7	7	0	0	0.0
Ragdoll	14	14	0	0	0.0
Scottish Fold	8	8	0	0	0.0
Sphynx	60	60	0	0	0.0
Unknown ^b	2	2	0	0	0.0
Total	3757	2617	1045	95	30.3
Total without Maine Coon	1013	1012	1	0	<0.1

^a Heterozygous and homozygous mutated.

^b No breed information, N: number of cats, G93C: guanine 93 to cytosine, MYBPC3: Myosin Binding Protein C 3, wild-type homozygous: G/G, heterozygous: G/C, mutated homozygous: C/C.

homozygous mutated cats, the penetrance was 71%. Compared with wild-type cats, mutated cats were significantly overrepresented in the affected (HCM) feline group ($P = 0.003$, Table 2): 18% (10/55) of

Table 2 Distribution of the 164 Maine Coon cats that underwent echocardiography (Echo-Group) according to their genotype (MYBPC3-A31P mutation) and phenotype (hypertrophic cardiomyopathy).

Echo-Group	G/G	G/C	C/C	Total	Phenotype%
Unaffected	107	43	2	152	93
Affected	2	5	5	12	7
Total	109	48	7	164	
Genotype%	66	30	4		
Carriers%		34			

G/G: wild-type homozygous, G/C: heterozygous, C/C: mutated homozygous, Affected and Unaffected: cats with or without hypertrophic cardiomyopathy respectively, Phenotype%: distribution between unaffected and affected cats, Genotype%: distribution between homozygous wild-type, heterozygous and homozygous mutated cats, Carriers%: genetic prevalence of the mutation (heterozygous and homozygous mutated cats).

mutated cats were diagnosed with HCM, representing more than 83% (10/12) of affected cats (equally divided between heterozygous and homozygous mutated), while only 2% (2/109) of the wild-type cats were affected by the disease (representing 17% of the affected cats). MYBPC3-A31P mutation was therefore significantly associated with an increased risk of HCM [RR = 9.91, CI 95% = 2.1–46.8]. The risk increased when cats were homozygous for the mutation [RR = 35.50, CI 95% = 5.8–216.7]. Among mutated Maine Coon cats with HCM ($n = 10$), the number of animals with congestive heart failure was similar (1 homozygous mutated and 1 heterozygous cat).

The mean age of the 164 cats from the Echo-Group was 2.6 ± 2.0 years (0.3–11.5 years, Table 3). The age of unaffected cats carrying the MYBPC3-A31P mutation varied between 0.3 and 11.5 years, while the age of diseased cats varied between 0.8 and 4.6 years. Ages of affected and unaffected cats that carried the MYBPC3-A31P mutation were not statistically different ($P = 0.771$). The percentage of males in the Echo-Group was 37% (60/164) while 67% (8/12) of the affected cats were males (Table 4).

Discussion

The present study provides data on the genetic prevalence of the MYBPC3-A31P mutation in a large cohort of cats with or without a known phenotypic status. In this report, the prevalence of the mutation and the prevalence of HCM were also compared in order to associate the genotype and the phenotype in a population of Maine Coon cats (Echo-Group).

In the first step of our study, the percentage of Maine Coon cats carrying the MYBPC3-A31P mutation was 41.5%. This prevalence seems to be higher than that estimated by Fries et al. (34%).¹⁵ The difference may be explained by the geographic origin of the cohorts: all Maine Coon cats recruited in our study came from Europe, whereas, in the report by Fries et al., four continents (North America, Europe, Asia, and Australia) were represented with most cases coming from the United States. In their study, the percentage of European Maine Coon cats that had at least 1 copy of the mutation was 37.6%. So it appears that the estimates from the two studies with regard to prevalence of the mutation in Europe are the same or at least similar.

Persian, British Shorthair, Sphynx, Ragdoll and several other feline breeds are also affected by HCM.²⁰ This is the reason why we decided to screen a large population of cats from 16 different breeds other than Maine Coon ($n = 1013$). None of these

Table 3 Age distribution of the 164 Maine Coon cats that underwent echocardiography (Echo-Group) according to their genotype and phenotype.

Echo-Group	Age (years) Mean \pm SD [range]			
	G/G	G/C	C/C	All
Unaffected cats	2.4 \pm 1.7 [0.4–9.0] (n = 107)	3.1 \pm 2.8 [0.3–11.5] (n = 43)	3.3 \pm 0.4 [3.0–3.6] (n = 2)	2.6 \pm 2.1 [0.3–11.5] (n = 152)
Affected cats	0.9 \pm 0.1 [0.8–1.0] (n = 2)	3.3 \pm 0.9 [2.5–4.5] (n = 5)	2.4 \pm 1.5 [1.2–4.6] (n = 5)	2.6 \pm 1.4 [0.8–4.6] (n = 12)
All	2.4 \pm 1.7 [0.4–9.0] (n = 109)	3.2 \pm 2.6 [0.3–11.5] (n = 48)	2.7 \pm 1.3 [1.2–4.6] (n = 7)	2.6 \pm 2.0 [0.3–11.5] (n = 164)

Mean age: years, G/G: wild-type homozygous, G/C: heterozygous, C/C: mutated homozygous, Affected and Unaffected: cats with or without hypertrophic cardiomyopathy, respectively.

1013 cats was positive for the mutation, except for one British Longhair cat (heterozygous). Fries et al. also found the mutation in one Ragdoll and one Siberian cat.¹⁵ The presence of the mutation in these 3 cats represents a punctual inconsistency and may be due to fortuitous crossbreeding. Ragdoll, Siberian, British Longhair and Maine Coon are longhair breeds. It is possible that crossbreeding occurred in their histories, and that these 3 cats had a Maine Coon cat in their lineage. A de novo mutation of the *MYBPC3* gene may also explain these 3 cases, but this hypothesis remains less probable. A haplotype analysis might demonstrate that the mutation found in these cats is the same. Nevertheless, the *MYBPC3*-A31P mutation can be considered as specific to the Maine Coon breed, with some potential marginal events.

Different prevalence values, depending on the echocardiographic ranges used, were obtained in a Swedish study in which 42 asymptomatic Maine Coon cats were evaluated for HCM by echocardiography.¹⁷ Prevalence varied from 9.5 to 26.2% when the upper reference values of LVFW or IVS thickness varied from 6.0 mm or 5.0 mm. Chetboul and collaborators also reported a marked within-day and between-day intra- and inter-observer variability according to the observers' experience, and its influence on conventional echocardiographic measurements in the cat.¹⁸ In the present study, the cats were deliberately screened in a single cardiologic center involving validated observers and methods so as to limit the influence of intra- and inter-observer variability. Using this diagnostic protocol, the prevalence of HCM in Maine Coon cats with a mean age of 3 years was shown to be less than 10%. This prevalence of 1 in 10 in Maine Coon breed is markedly higher than the estimate of 1 in 500 people.⁴

In the Echo-Group, a marked difference was found between the phenotype and the genetic status. In the 164 Maine Coon cats from the Echo-Group, 34% carried the mutation, while only 7% were HCM-

affected. However, the prevalence of HCM may have been underestimated due to the young age of the recruited cats and this is the main limitation of the present study. Echocardiographic examinations were indeed most often requested by breeders who wished to screen the youngest cats in their cattery in order to obtain an early diagnosis for HCM, and adapt their breeding programs accordingly.

The first clinical signs of HCM were reported to usually occur between 1.5 and 3 years of age in Maine Coon cats with complete penetrance.¹³ However, one heterozygous female did not have any symptom of HCM at 7 years of age in the Kittleson et al.'s colony.¹⁴ Similarly, in the present study, 42% of unaffected mutated cats were over 3 years of age [3.0–11.5]. In particular, 1 male and 2 females were more than 10 years old. However, in the present study, no difference was observed between the ages of affected and unaffected carriers of the A31P mutation, which suggests incomplete penetrance. Furthermore, homozygous mutated cats have been reported to show HCM symptoms earlier than heterozygous ones,¹⁴ but this was not the case in the present study. These data suggest that unaffected mutated cats, in particular, need to be followed up to determine whether and when HCM occurs or when the first tissue Doppler imaging signs appear in asymptomatic cats.^{16,21,22}

In humans, symptoms of HCM are heterogeneous even when mutations occur in the same gene.²³ Mutations in *MYBPC3* lead mainly to truncation of the protein which gives a relatively mild phenotype, but mutations in *MYBPC3* are also correlated with severe phenotypes.^{24,25} Our data suggest that the G93C mutation in *MYBPC3* may be associated with an incomplete penetrance in the Maine Coon breed. As in humans, this incomplete penetrance could be explained by multiple genetic and/or environmental modifiers impacting the phenotype of cats from the Echo-Group whereas cats from Kittleson's colony were strongly inbred and probably lived under similar conditions.

Table 4 Distribution the 164 Maine Coon cats that underwent echocardiography (Echo-Group) according to their genotype, phenotype, and gender.

Echo-Group	G/G	G/C	C/C	Total	Phenotype%	Age (years) Mean \pm SD [range]
Unaffected M	40	12	0	52	32	2.8 \pm 2.2 [0.3–11.5]
Affected M	2	4	2	8	5	2.1 \pm 1.1 [0.8–4.0]
Total	42	16	2	60	37	
Genotype% M	26	9	1	37		
Mean age \pm SD [range]	2.5 \pm 2.0 [0.6–8.9]	3.4 \pm 2.5 [0.3–11.5]	1.5 \pm 0.1 [1.4–1.5]			
Unaffected F	67	31	2	100	61	2.5 \pm 2.0 [0.4–10.5]
Affected F	0	1	3	4	2	3.4 \pm 1.6 [1.2–4.6]
Total	67	32	5	104	63	
Genotype% F	41	20	3	63		
Mean age \pm SD [range]	2.3 \pm 1.6 [0.4–9.0]	3.0 \pm 2.7 [0.5–10.5]	3.2 \pm 1.3 [1.2–4.6]			
Total	109	48	7	164		2.6 \pm 2.0 [0.3–11.5]

M: male, F: female, G/G: wild-type homozygous, G/C: heterozygous, C/C: mutated homozygous, Affected and Unaffected: cats with or without HCM, Phenotype%: distribution between unaffected and affected cats, Genotype%: distribution between homozygous wild-type, heterozygous and homozygous mutated cats.

In the present study, although a minority of mutated cats was affected by HCM (18%), as expected, mutated cats were overrepresented among the diseased animals (83%). However, HCM was also diagnosed in 2 homozygous wild-type Maine Coon cats with a mean age of 0.9 years. This suggests an etiological heterogeneity for HCM in the Maine Coon breed. In 2007, a novel *MYBPC3* mutation, R820W, was identified in Ragdoll cats.²⁶ This mutation occurs in a different domain to that of the Maine Coon cat mutation and the phenotype seems to be more severe than in Maine Coon cats. In the present study, no Maine Coon cat carried this second mutation, contrary to Ragdoll cats (data not shown). *MYBPC3* is one of the most commonly mutated genes in human HCM, and more than 140 causative mutations have been identified in this sarcomeric gene.⁶ As in humans, it can be hypothesized that other mutations in *MYBPC3* or in other sarcomeric genes may also be responsible for HCM in the Maine Coon breed.

Finally, although few Maine Coon cats were affected by HCM ($n = 12$) in our study, most of them (67%) were males. The overrepresentation of affected males in the feline species and in the Maine Coon breed has already been discussed.^{27,28} Factors like modifier genes or hormones may have a bearing on the sexual predisposition to HCM as has been reported in humans with HCM or other heart diseases.^{29,30}

In conclusion, the *MYBPC3*-A31P mutation is highly prevalent in European Maine Coon cats and seems specific to this feline breed although potential marginal events may occur. The majority of affected Maine Coon cats carry one or two copies of the A31P mutation, suggesting a strong causative relationship between this mutation and HCM in the Maine Coon breed. The prevalence of HCM in cats homozygous for the mutation is much higher than in cats heterozygous for the mutation. However, the disease penetrance at 2.6 years is incomplete. Lastly, as several affected cats are homozygous wild-type for the mutation, it is highly likely that other causes (genetic or not) are also responsible for the disease in the Maine Coon breed.

Conflicts of interest

None.

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