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Detection of Polymorphism of Myosin-Binding Protein C3 (MYBPC3) Gene in Persian Breed Cat with and without Hypertrophic Cardiomyopathy

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Abstract

Background: In cats, the hypertrophic cardiomyopathy (HCM) has been known as a prevailing heart disease. The mutations being causative in the gene that encods cardiac myosin binding protein C (MYBPC3) are found in the Ragdoll and Maine Coon breeds.

Objectives: HCM is believed to be hereditary in other breeds too.

Methods: Blood samples were collected for DNA extraction from two unaffected and seven affected Persian breed cats with HCM. Conventional PCR was performed. Also, DNA sequencing was performed, and the sequence changes were used to detect single nucleotide polymorphisms in the MYBPC3 gene and predict amino acid substitutions based on the Acc. No. (XM_019812396.1) and comparisons with the literature on identified breed variants and control samples.

Results: Although many single nucleotide polymorphisms were found in both affected and unaffected Persian cats, no causative mutation for HCM was observed.

Conclusions: In this breed, HCM does not seem to be caused solely by mutations in this cardiac gene. Potential cardiac genes should be investigated to uncover other genetic reasons for this cardiac disease in the Persian cat breed.

Keywords: Hypertrophic cardiomyopathy, Myosin-binding protein C3, Persian Breed, Cat, PCR

Introduction

Hypertrophic cardiomyopathy (HCM) has been defined as left ventricular myocardium hypertrophy not attributed to an existing disease or anomaly. In humans, however, HCM is a widely known disease but it is especially common in cats. HCM is so often an occult disease, which can result in potentially fatal complications. In cats, it is the highly occuring heart disease, impacting approximately 15% of their population (Payne *et al*., 2015). It is frequently related to specific breeds, including Ragdoll, Maine Coon, and British Shorthair (Meurs *et al*., 2007). However, most patients are non-breed domestic cats (Côté *et al*., 2011).

In addition, the diagnosis of heart abnormalities by cardiac auscultation alone is difficult. Therefore, para-clinical examinations, such as radiography and echocardiography, are necessary to confirm the diagnosis (Sadri *et al*., 2022).

47 Limited treatment options are available in cats, and the cats with symptoms show a poor
48 prognosis. It leads to underscoring the importance of etiology knowledge, which can be
49 indicated as measures for prevention. HCM is associated with a genetic defect underlying in
50 humans, and it is accepted as a typical case in cats as well. However, the genetic variant causing
51 the disease stays usually unrevealed in cats, whereas only two variants that are breed-specific
52 have been identified (Schipper *et al*., 2019).
53 In some breeds, including Domestic Shorthairs, a genetic etiology is suspected (Côté *et al*.,
54 2011). In cats, however, only two variants being causative in MYBPC3 are detected; in Maine
55 Coons the XM_019812396.1:c.91G > C (Meurs et al., 2005), and in Ragdolls the c.2455C > T
56 (Meurs *et al.,* 2007). In humans, HCM is caused by the latter variant ortholog (Schipper *et al*.,
57 2019).

58 MYBPC3 (known as human geneID: 4607) is composed of 33 exons that can encode protein C of
59 1274 amino acids binding cardiac myosin. Apparently, the protein is crucial in controlling
60 sarcomeric contractility and could also influence sarcomere architecture (Gupta *et al*., 2014).
61 The widely known variants as causative in MYBPC3 cab be either truncating or missense (Walsh
62 *et al*., 2017a).

HCM, in human, is a relatively complex disease whose pathogenesis, genetics, and modifying factors all still require to be completely determined. However, currently, the limited knowledge of feline HCM is available, but suggests many similarities existing between species.

In cats, a wider knowledge of the genetic aspect regarding HCM would allow to screen the genetic of breeding animals more comprehensive. Then, the breeders can restrict the spread of variants causing disease in the population of cat, and the HCM incidence is reduced.

Given the importance of cats as pets and the popularity of the Persian breed among owners in Iran, the present study is the first on genetic hypertrophic cardiomyopathy in cats in Iran.

Based on these considerations, The aim of present study is to determine the variants causing disease in Persian cats that are affected, with application of MYBPC3 gene analysis, being selected due to its significance in human HCM.

Materials and Methods

Patient selection

From September 2020 to March 2022, Persian breed cats were presented to the Small Animal Hospital of the Veterinary Medicine Faculty, Tehran University, for cardiovascular examination

and follow-up if previously diagnosed with HCM or had significant cardiopulmonary clinical signs. Based on the general examination, auscultation of lung and heart sounds, ECG evaluation, and Doppler blood pressure measurement, hypertrophic cardiomyopathy (HCM) was suspected. They were referred to the diagnostic imaging department for chest radiography and echocardiography for evidence of hypertrophic cardiomyopathy (HCM) if left ventricular free wall thickness in diastole (LVFWd) and interventricular septum in diastole (IVSd) were > 6 mm or both were detected by M-mode echocardiography (Figure 1).

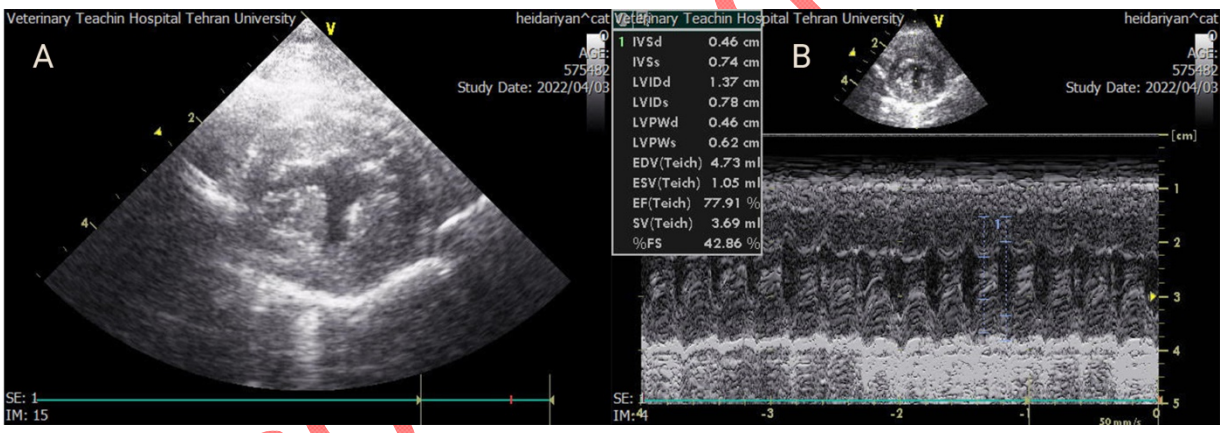

Figure 1. (A) Two-dimensional echocardiographic image of a cat with HCM, (B) M-mode echocardiographic measurement of left ventricular free wall thickness (LVFWd) and interventricular septum (IVSd) > 6 (mm)

89 Once HCM cases were identified on echocardiographic studies, other causes of left ventricular
90 hypertrophy in cats, such as renal failure, hyperthyroidism, and elevated blood pressure, were
91 excluded by screening renal levels (BUN, Scr), thyroid levels (TT4), and Doppler blood pressure.
92 Finally, two groups of cases were selected: seven affected cats (3 females and 4 males, ranging
93 2 to 8 years old, with 5.5 years old as mean age) with HCM and two healthy cats (unaffected) (1
94 male and 1 female, aged 2-4 years old, with 3 years old as mean age) (Table 1). For all cases,
95 blood samples were collected in EDTA tubes and kept at -18 C° till DNA extraction.

96 Table 1. Phenotypic information for HCM-affected and non-affected Persian cats breed.

HCM-affected	Age (year)	Gender	*IVSD (mm)	LVFWD (mm)	Renal panel		Thyroid panel	BP (mmhg)
					BUN (mg/dl)	Scr (mg/dl)	TT4 (mcg/dl)	
1	8	F	6	13	28	1.2	6.5	120

2	7	M	8.5	12	30	1.37	5.5	130
3	2	M	6.6	8	23	1.31	8	100
4	4	F	5.1	10	19.6	1.4	7.5	120
5	3	M	6	6.2	23	1.8	5.8	100
6	8	F	6	8.3	24	1.6	6.8	130
7	6	M	8.7	6.7	25	1.8	5.8	140
Non-affected								
1	4	F	3.2	5.5	32	1.2	6.2	100
2	2	M	4.3	3.8	30	1.3	5.8	100

97

98 *IVSd: Interventricular septum in diastole, LVFWd: Left ventricular free wall thickness in
99 diastole, BUN: Blood urea nitrogen, Scr: Serum creatinine, TT4: Total thyroxine, BP: Blood
100 pressure, F: Female and M: Male

101 *Primer design*

102 In cats, assembly of the *felis catus* (Acc. No.: XM_019812396.1) was employed to identify where
103 the exons are located, and the MYBPC3 gene sequence. The selected primers in the present
104 study were from Schipper *et al.,* (2019), and many primers were designed based on the Acc. No.
105 (XM_019812396.1) using the PRIMER 3 software (Table 2) (Schipper *et al*., 2019).

106 Table 2. Selected PCR primers for detection of polymorphism in MYBPC3 gene

Exon	Forward	Reverse	Reference
1	TCAGAAGGATGGGAAGGAGAAACCAAGA	GGTTGGGCAAGAGGCAGATAAGAAATCC	Schipper *et al.,* (2019)
2	TCAGCCAAAGCAAAGGCGAGACA	CCAGGAAGGAAGGGTCAGGTATCCAA	Schipper *et al.,* (2019)

6	ACCCCACATTCTGAGCCTTTCCA	CTCCTCCCACTCTTCCACAGTCTT	Schipper *et al.*, (2019)
7,8,9	GACAGACAGGGAAATTGGTTTAGAGAGGT	CAAGGGTCATGGATGGGCAGGT	Schipper *et al.*, (2019)
13,14	TCTGGCACTCACCACTTGACCT	CCACGGCGATGCGTGTGA	Schipper *et al.*, (2019)

DNA extraction

In all cases, the samples of blood were collected to extract their DNA. DNA extraction was conducted utilizing a DNA extraction kit, commercially available, following the instructions of

manufacturer (Sinaclon, EX6071, Iran) (Ghalyanchilangeroudi *et al.,* 2021). It was recommended to keep extracted DNA at -20 C°.

Conventional PCR

Polymerase chain reaction (PCR) was carried out in 25 µl as final volume by a 2 × master mix, being ready-to-use, which contained 0.2 mM of each dNTP, 2 mM MgCl2, 2 U Taq DNA polymerase, 10× PCR buffer (Sinaclon, Iran), along with 1 µl 10 pmol concentration of each primer (Sinaclon, Iran). The thermal conditions included: initial denaturation for 5 min at 95 C°, then 35 cycles of 95 C° for 30 s, 52 C° for 30 s, 72 C° for 1 min, and a final extension for 7 min at 72 C°. The analysis of PCR product was performed using electrophoresis on a 1.5% agarose gel, and then illustrated under UV light. The PCR results were later examined to identify the nucleotide sequences (Peighambari *et al.*, 2022).

Partial sequencing

All PCR products with sufficient amplification of the correct fragment were taken for Sanger sequencing. The quality of the sequences was assessed individually using Chromass 2.6.5 software. CLC viewer 8.0 was used to examine nucleotide and amino acid sequences. The splice site and exonic sequences of the gene of feline MYBPC3 were obtained from feline contigs

utilizing NCBI blast function and prior studies. The nucleotide sequences were compared to the published normal feline sequence from the feline contigs, as well as previously described mutations in Ragdoll and Maine Coon cats.

Results

In this study, positive PCR results were obtained for the detection of the polymorphism of the MYBPC3 gene. This research's partial MYBPC3 gene sequences were deposited in GenBank with No: NC018732.3 (Table 3).

Table 3. The position of the exons was sequenced using the accession numbers to which the sequences were compared.

Exon	Map of target (Location)	Accession numbers
1	101341929-101342043	XM_019812396.1
2	101340571-101340837	XM_019812396.1
6	101338545-101338662	XM_019812396.1
7	101337987-101338035	XM_019812396.1

8	101337779-101337808	XM_019812396.1
9	101337568-101337621	XM_019812396.1
13	101335576-101335708	XM_019812396.1

137

138

139 Sequencing of exons 1, 2, 8, and 9 revealed no single base pair change in all affected and
140 unaffected control cats; a single nucleotide polymorphism (SNP) change was, however, spotted
141 in exon 6 (c.866 A > G) in 3 cats and 13 (c.677 C > A) in 2 cats with HCM and 7 (c.803 C > T) in 1
142 affected and 1 unaffected cat (Figure 2).

143

144 Figure 2. (A) Exon 1 and (B) Exon 2 sequencing and single nucleotide polymorphism (SNP)

145 detection in HCM-affected (H) and unaffected (N) Persian cats

146

147 In this study, although several SNPs were detected in the gene analyzed, they did not segregate
148 with the disease or alter the amino acid.

149 The previously reported mutations in the MYBPC3 gene in Ragdoll and Maine Coon cats were
150 not detected in any of the affected or unaffected cats in the study.

151

152

153 **Discussion**

154 In study of Schipper *et al.,* (2019), 27 variants were found in MYBPC3, of which 17 were
155 synonymous, and 10 were missense. The variant c.175G > A p. (Ala59Thr) in exon 2 was found
156 in 1 Maine Coon and 3 DSH cats, the c.220G > A p. (Ala74Thr) in exon 2 in 1 Ragdoll, 1 Maine
157 Coon, 2 BSH, and 7 DSH cats, the c.222C > T p, (Ala74=) in exon 2 in 1 Maine Coon and 2 DSH
158 cats, the c. 720C > T p. (Ser240=) in exon 6 in 1 DSH cat, the c. 772G > A p. (Val258Ile) in exon 7
159 in 7 DSH, 2 BSH, 1 Ragdoll, and 1 DSH × Persian cats, and the c.1140G > C p.(Arg380=) in exon
160 13 in 1 DSH cat, not in line with the present research result in the MYPBC3 gene.

Longeri *et al.,* (2013) were reported a substitution p.(Ala74Thr) in Maine Coons with HCM, not matching the present research's variants in the MYPBC3 gene.

In cats with HCM, Meurs *et al.,* (2009) explained eight variants in MYBC3. However, the annotation is slightly not clear, the variants could possibly be c.220G > A or c.222C > T (exon 2), c.772G > A (exon 7), c.1032C > T, c.1956C > T, c.2607C > T, c.2765C > T, and c.3109G > A, as Schipper *et al.,* (2019) explained.

No definitive conclusions, however, can be achieved about these variants since Meurs *et al.,* (2009) refused to explain them at the nucleotide level. The one explained as eighth variant by Meurs *et al.,* (2009) could be related to none of variants reported by Schipper *et al.,* (2019).

In study of Schipper *et al.,* (2019), 10 missense variants, potentially pathogenic, were detected in MYBPC3. In order to evaluate their pathogenicity, the amino acid substitution impacts were anticipated in silico, and the conservation of the amino acid, being affected, was evaluated. The substitution of Ala59Thr, Ala74Thr in exon 2, and V258Ile in exon 7 caused by missense variants in MYPBC3 were benign (based on the PROVEN, PolyPhen-2: HumDiv and HumVar and ConSurf score).

There are over 1500 HCM-causing mutations in humans, mostly found in sarcomeric genes; however, pathogenic variants in genes being non-sarcomeric, such as those calcium signaling proteins or encoding Z-disk proteins, have also been identified (Walsh *et al*., 2017b). The MYBPC3 gene is most usually related to HCM in humans, accounting for 40% of cases, followed by the MYH7 gene (Carrier *et al*., 2015). In the MYBPC3 gene, only two mutations have been explained in cats, although the sequence present in this gene has been largely conserved in mammals (cow, dog, human, mouse, rat) (Maron *et al*., 2015; Kittleson *et al*., 2015). Numerous investigations have been conducted based on sequencing the MYBPC3 gene fragment where this variant appears. The populations examined were mostly Maine Coon cats either with or without HCM, even though some belonging to other breeds were examined (up to 3757 cats belonging to 17 breeds) as well. The p.A31P mutation has been identified in both affected and unaffected Maine Coon cats; in other breeds, only three cases have been isolated and reported: a Siberian, a Ragdoll, and a British longhair cat (Gil-Ortuño *et al.,* 2020).

The SNPs in the cats investigated here did not meet the threshold for a causative mutation since they did not affect the amino acid produced nor segregate with the disease consistently. Nevertheless, through linkage analysis or broader relationship studies, these SNPs could be proven effective in future research of familial feline HCM in various cat breeds.

193 The absence of a mutation in this MYBC3 gene region does not rule out its potential role in this
194 disease in the Persian cat since a causative mutation may occur in the promoter or untranslated
195 areas of this gene. The cats studied could still have family feline HCM caused by a mutation in
196 one of the other HCM genes in humans, or they could have a mutation in a gene not yet linked
197 to HCM. Finally, possibly these cats' sickness has a distinct etiology.

198 To summarize, felines are the natural model of HCM that mimics the genotype and phenotype
199 of human. The cat is the ideal species to investigate the efficacy of new genetic and preventive
200 therapies due to its life expectancy, typically about 16 years, and the disease's typical early
201 onset between 3 and 5 years old (Gil-Ortuño *et al.,* 2020; Sleeper *et al.,* 2009). All of this should
202 motivate researchers to use cutting-edge techniques of genetic sequencing to examine HCM in
203 cats. Collaboration between doctors and veterinarians could benefit both species, humans and
204 cats, affected by this dreadful disease.

205 *Conclusion*

206 In particular breeds (Ragdoll and Main Coon, respectively), there are only two genetic variants
207 as founder related to feline HCM (p.R820W and p.A31P), both in the MYBPC3 gene. The
208 detected variants, in high frequency, in unaffected cats support the idea of a minor to
209 moderate effect on phenotype and the probable interplay with other environmental or genetic

factors. Other breeds' genetic causes of HCM are unknown. Since the disease is similar in humans and cats, felines are an ideal model for developing new corrective and preventive therapies for human and feline HCM (Gil-Ortuño *et al.,* 2020; Prondzynski *et al.,* 2019; Ammirati *et al.,* 2016). The investigation of the genetic origin of feline HCM should use new genetic testing methods.

Conflict of interest

The authors declare no conflict of interest.

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تشخیص وقوع پلی مورفیسم ژن پروتئین میوزین بایندینگ C3 (MYBPC3) در گربه های نژاد پرشین با و بدون کاردیومیوپاتی هایپرتروفیک

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چکیده فارسی

زمینه مطالعه: کاردیومیوپاتی هایپرتروفیک (HCM) یک بیماری قلبی شایع در گربه ها است. جهش های ایجادکننده بیماری در ژن میوزین بایندینگ C3 در گربه های نژاد مین کون و رگدال شناسایی شده است. به نظر می رسد که بیماری کاردیومیوپاتی هایپرتروفیک در سایر نژادها نیز زمینه ارثی داشته باشد.

هدف: هدف از این مطالعه شناسایی واریانت های ژنتیکی عامل بیماری کاردیومیوپاتی هایپرتروفیک در ژن میوزین بایندینگ C3 در گربه های نژاد پرشین در ایران می باشد.

روش کار: نمونه خون کامل برای استخراج DNA از دو گروه گربه نژاد پرشین مبتلا به کاردیومیوپاتی هایپرتروفیک و سالم جمع آوری شد. واکنش زنجیره ای پلیمراز استاندارد و همچنین توالی یابی بر روی قسمتی از ژن میوزین بایندینگ C3 نمونه های گروه های بیمار و سالم انجام شد. تغییرات توالی برای تشخیص پلی مورفیسم ژن و پیش بینی جایگزینی آمینواسید بر اساس شماره شناسه (XM_019812396.1) و مقایسه نتایج با جهش های شناخته شده قبلی در مقالات و نمونه های کنترل مورد بررسی قرارگرفت.

نتایج: اگرچه تعدادی جهش تک نقطه ای در هر دو گروه سالم و درگیر بیماری یافت شد اما هیچ جهش ایجاد کننده کاردیومیوپاتی هایپرتروفیک گزارش نشد.

نتیجه گیری نهایی: در این نژاد، بیماری کاردیومیوپاتی هایپرتروفیک به نظر نمی رسد به تنهایی توسط جهش ها در این ژن ایجاد شود. ژن های قلبی دیگر برای شناسایی عوامل ژنتیکی بیماری کاردیومیوپاتی هایپرتروفیک باید مورد بررسی قرار گیرند.

کلمات کلیدی: کاردیومیوپاتی هایپرتروفیک، پروتئین میوزین بایندینگ C3، نژاد پرشین، گربه، واکنش زنجیره ای پلیمراز