Journal of Veterinary Cardiology (2015) **17**, S53—S73

ELSEVIER

Journal of Veterinary Cardiology
ESVC

www.elsevier.com/locate/jvc

REVIEW

The genetic basis of hypertrophic cardiomyopathy in cats and humans☆

Mark D. Kittleson, DVM, PhD [a,*], Kathryn M. Meurs, DVM, PhD [b], Samantha P. Harris, PhD [c]

[a] *Department of Medicine and Epidemiology, University of California, Davis, Davis, CA 95616, USA*
[b] *Department of Veterinary Clinical Sciences, North Carolina State University, Raleigh, NC 27607, USA*
[c] *Department of Cellular and Molecular Medicine, University of Arizona, Tucson, AZ 85721, USA*

Received 9 July 2014; received in revised form 16 January 2015; accepted 16 March 2015

KEYWORDS
Feline;
Myosin binding protein C;
Mutation

Abstract Mutations in genes that encode for muscle sarcomeric proteins have been identified in humans and two breeds of domestic cats with hypertrophic cardiomyopathy (HCM). This article reviews the history, genetics, and pathogenesis of HCM in the two species in order to give veterinarians a perspective on the genetics of HCM.

Hypertrophic cardiomyopathy in people is a genetic disease that has been called a disease of the sarcomere because the preponderance of mutations identified that cause HCM are in genes that encode for sarcomeric proteins (Maron and Maron, 2013). Sarcomeres are the basic contractile units of muscle and thus sarcomeric proteins are responsible for the strength, speed, and extent of muscle contraction. In people with HCM, the two most common genes affected by HCM mutations are the myosin heavy chain gene (MYH7), the gene that encodes for the motor protein β-myosin heavy chain (the sarcomeric protein that splits ATP to generate force), and the cardiac myosin binding protein-C gene (MYBPC3), a gene that encodes for the closely related structural and regulatory protein, cardiac myosin binding

☆ A unique aspect of the Journal of Veterinary Cardiology is the emphasis of additional web-based materials permitting the detailing of procedures and diagnostics. These materials can be viewed (by those readers with subscription access) by going to http://www.sciencedirect.com/science/journal/17602734. The issue to be viewed is clicked and the available PDF and image downloading is available via the Summary Plus link. The supplementary material for a given article appears at the end of the page. To view the material is to go to http://www.doi.org and enter the doi number unique to this paper which is indicated at the end of the manuscript.

* Corresponding author.
E-mail address: mdkittleson@ucdavis.edu (M.D. Kittleson).

http://dx.doi.org/10.1016/j.jvc.2015.03.001

protein-C (cMyBP-C). To date, the two mutations linked to HCM in domestic cats (one each in Maine Coon and Ragdoll breeds) also occur in MYBPC3 (Meurs et al., 2005, 2007). This is a review of the genetics of HCM in both humans and domestic cats that focuses on the aspects of human genetics that are germane to veterinarians and on all aspects of feline HCM genetics.

Abbreviations

cMyBP-C	cardiac myosin binding protein-C
HCM	hypertrophic cardiomyopathy
LV	left ventricle
MYBPC3	cardiac myosin binding protein C gene
MYH7	β-myosin heavy chain gene
RFLP	restriction fragment length polymorphism
SAM	systolic anterior motion of the mitral valve
TDI	tissue Doppler imaging
UPS	ubiquitin—proteasome system

Human hypertrophic cardiomyopathy

Definition and etiology

The definition of hypertrophic cardiomyopathy (HCM) has evolved as the clinical understanding and the genetic underpinnings of the disease have unfolded. In general terms, HCM is a primary myocardial disease that most commonly causes thickening of the left ventricular (LV) myocardium (either regional asymmetric thickening or concentric thickening/hypertrophy) in the absence of other cardiovascular or systemic causes.[4] Wall thickening is thus not secondary to pressure overload (e.g., hypertension, aortic stenosis) or hormonal stimuli (e.g., thyroid disease), but is a primary abnormality of the heart muscle itself. Hypertrophic cardiomyopathy is also distinct from other genetic diseases that can cause LV hypertrophy in humans, especially in childhood, such as Noonan syndrome or Danon's disease.[5–7]

Hypertrophic cardiomyopathy in humans is most commonly caused by mutations in genes that encode for the proteins that make up the cardiac muscle sarcomere or in proteins closely associated with sarcomere function (Fig. 1). Mutations in 11 sarcomeric genes have thus far been linked to HCM and account for about 70% of the cases seen in human patients.[8] That leaves a cause to be identified in approximately 30% of human patients with unexplained LV wall thickening (i.e. HCM not attributable to other systemic causes).[4] In these cases the disease may be attributable to novel mutations in either non-coding gene sequences or in other proteins closely associated with sarcomere function such as calcium handling proteins.[9] Most mutations are "private" meaning that they are unique to a single family or individual and >1400 distinct gene variants have been identified in patients with HCM.[1] Most of the mutations are missense mutations in which one highly conserved DNA nucleotide is replaced by a different nucleotide resulting in a different codon. A different codon (See supplemental Table A for definition) may or may not produce a different amino acid but if it does, inclusion of that altered amino acid can disrupt function of that protein which may lead to a disease such as HCM. When a mutation causes a disease (e.g., HCM) it does produce a different amino acid, which forms an abnormal protein.[8]

Humans with sarcomeric gene mutations express a wide range of phenotypes from no apparent disease to massive wall thickening and a wide range of clinical outcomes from no disease sequelae to sudden death and heart failure. The vast intergeneic and intragenic heterogeneity seen in humans with HCM likely accounts for much of the breadth of these clinical outcomes and probably also accounts for at least some of the variability in the amount of hypertrophy from patient to patient. However, left ventricular hypertrophy is not the only important manifestation of the disease. It is now clear that some sarcomeric mutations cause little or no LV hypertrophy per se, but nonetheless lead to other common sequelae of the disease including diastolic dysfunction, arrhythmia, and sudden cardiac death.[10] For instance, mutations in the cardiac troponin T gene commonly predispose patients to sudden death, even if only mild hypertrophy is present.[11]

In addition to the sarcomeric gene mutations, mutations in other genes occasionally have been suggested as causative for HCM in humans. They include mutations in genes that encode for