

File ID 157784  
Filename Summary

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SOURCE (OR PART OF THE FOLLOWING SOURCE):

Type Dissertation  
Title Genetic basis of hypertrophic cardiomyopathy  
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Faculty Faculty of Medicine  
Year 2010  
Pages 192  
ISBN 978-90-9024905-6

FULL BIBLIOGRAPHIC DETAILS:

<http://dare.uva.nl/record/325896>

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# Summary



Hypertrophic cardiomyopathy (HCM) is a disease characterized phenotypically by unexplained left ventricular hypertrophy in the absence of an underlying cause. With a prevalence of 1 in 500 individuals, HCM is the most common heritable cardiac disease and the most common cause of sudden cardiac death in young adults, especially athletes. Pathologically, HCM is characterized by microscopic cardiomyocyte hypertrophy, myofibrillar disarray and focal, interstitial fibrosis. Genetically, HCM was considered a disease of the sarcomere, or more specifically the cardiac myofilaments, with most mutations thus far found in genes encoding cardiac myofilaments. However, among different international cohorts, the yield of genetic testing for these genes, now equivalent to commercial genetic tests, ranged between 30 and 70%. More recently, it was demonstrated that there was a strong correlation between ventricular septal morphology and the underlying genotype with 80% of reverse-curve HCM being genotype positive and only 8% of sigmoidal-HCM harboring a pathogenic mutation. Based on these findings, we set out to study the genetic basis of genotype negative HCM and study the genotype-phenotype correlations of newly discovered HCM-susceptibility genes.

Chapter 1 of this thesis is a general introduction on HCM which briefly reviews the clinical and genetic history of HCM. Furthermore, the state of genetics of HCM in 2007 and recent observation of correlation between septal contour and underlying genetic substrate are discussed. It also sets the stage for most chapters in this thesis and the discussion whether HCM is one disease or maybe a disease that can be categorized in various clinical, genetic or morphological subgroups.

Chapter 2 describes the discovery and subsequent genotype-phenotype analyses of mutations in three HCM-susceptibility genes that encode key cytoskeletal/scaffolding proteins of the Z-disc. As a large percentage of patients remained without genetic explanation for their disease, the research field moved from the myofilament proteins of the sarcomere to the sarcomere's Z-disc and its vast array of proteins as mutations had previously been published in dilated cardiomyopathy (DCM) or animal models supported a role for certain genes in the pathogenesis in HCM. We discovered that 4% of unrelated patients with HCM harbored mutations in *CSRFP3*-encoded muscle LIM protein (MLP) and *TCAP*-encoded telethonin (TCAP). Phenotypically these patients mirrored the phenotype seen in myofilament-HCM and patients were more affected than patients who continued to be genetically elusive.

Chapter 3 provides the first description of mutations in *ANKRD1*-encoded ankyrin repeat domain 1 (ANKRD1) (also known as cardiac ankyrin repeat protein (CARP)) associated with HCM. In this collaborative effort with our colleagues in Japan led by Dr. Akinori Kimura, we describe the discovery of 3 novel mutations in *ANKRD1* in two independent cohorts of unrelated patients with HCM. Furthermore, two mutations were found in the N2A-domain of the large sarcomere-stretching protein titin encoded by *TTN*. Functional analyses of these mutations demonstrated increased binding of titin to ANKRD1 as well as altered localization of ANKRD1-mutants in cardiomyocytes. Compared to wild type ANKRD1, which localizes to the striated pattern at the Z-I-bands, mutant ANKRD1 showed increased localization within or at nuclear membrane in approximately 60% of mature cardiomyocytes.

Chapters 4 and 5 describe genotype-phenotype correlations between the previously discovered, novel Z-disc associated HCM mutations and their relationship to sex (Chapter 5) and/or their underlying genotypic substrate. Akin to the strong correlations between reverse curve-HCM and the presence of a myofilament mutation, we found that Z-disc HCM is preferentially sigmoidal. Described in Chapter 4, we found that among the 13 patients with Z-disc HCM (including mutations in the novel HCM-associated gene alpha-actinin 2 encoded by *ACTN2*), 85% had a sigmoidal septal contour. None of the patients demonstrated the myofilament-associated reverse septal morphology. These findings led us to speculate that the pathogenic mechanism behind Z-disc HCM might predispose patient to the more sigmoidal septal bulge at the left ventricular outflow tract.

Chapter 5 focuses on this same subset of patients, but specifically focuses on the sex-related differences within this cohort. In a previous study involving genetically uncharacterized patients with HCM from the USA and Italy, women i) were older and more symptomatic at diagnosis, ii) had more left ventricular outflow tract obstruction, and iii) were more likely to progress to advanced heart failure and stroke. In our study, we performed a similar analysis on patients that were genotyped for mutations in the myofilament genes and scored for septal morphology on echocardiography. Similar to previous studies, we found striking differences between men and women, but these differences were confined largely to the subgroup of women with mutation-negative, sigmoidal HCM.

Multiple and linear regression models demonstrated that, for women, age at diagnosis, systolic blood pressure and presence of left ventricular outflow tract obstruction were directly dependent on sigmoidal morphology. These observations demonstrated that whereas mutations within the sarcomere appear to dominate the disease process, in their absence, sex has a significant modifying effect among patients with genotype negative, sigmoidal HCM.

In an effort to further explain genotype negative HCM, we subsequently moved away from the cardiac Z-disc to analyze a novel candidate gene, which in knock-out mice showed late onset HCM and a distinct gender predilection. Described in Chapter 6 is the discovery of 6 novel HCM-associated mutations in *TIEG1*-encoded TGF $\beta$ -inducible early gene-1 in two independent cohorts of unrelated patients with HCM from the Academic Medical Center (Amsterdam, NL) and the Mayo Clinic (Rochester, MN USA). Subsequent *in vitro* studies showed that, akin to data from the *TIEG1* knock-out mouse, 5 out of 6 *TIEG1*-mutations significantly altered *TIEG1* function on the *PTTG1*-promoter resulting in a significant upregulation of *PTTG1*-promoter activity. Immunohistochemistry analyses showed increased *PTTG1*-protein staining in HCM patients in general and even more in patients with *TIEG1*-HCM suggesting that up-regulation of *PTTG1* might be a final common pathway in HCM and a potential disease biomarker.

Chapter 7 is a recent review article describing the diagnostic, prognostic and therapeutic implications of genetic testing for HCM. Besides the past and present state of HCM genetics, it describes how genetic testing has now moved from the laboratory bench into the physician's hands at the patient's bedside. It provides physicians an algorithm on when to consider genetic testing and discusses guidelines for screening family members of patients with HCM. It also discussed the particular situation of screening children or athletes related to patients with HCM. Lastly, it provides insights in the current and future options for patients with genotyped HCM and examines where research is making strides to delineate the underpinnings of this disease.

In conclusion, the understanding of HCM has matured from its cornerstone as a disease of the sarcomere to a compendium of diseases with various clinical, genetic and morphologic substrates. Research has provided us more insights into i) the pathogenetic development of HCM, ii) the possible pro-hypertrophic pathways that are triggered, and iii) the modifiers that influence the disease phenotypes. These findings have opened the door for individualized medicine and the development of therapeutic trials aimed at disease prevention or slowing of disease progression in patients with genotype positive, hypertrophy negative HCM. However, far more research is needed to understand its exact pathogenic pathways, discover novel drug targets or understand and prevent its devastating feature of sudden cardiac death.