Genetic basis of hypertrophic cardiomyopathy
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Citation for published version (APA):
Bos, J. M. (2010). Genetic basis of hypertrophic cardiomyopathy

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Chapter 4

Echocardiographic-Determined Septal Morphology
in Z-Disc Hypertrophic Cardiomyopathy

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Biochem Biophys Res Commun 2006; 351(4): 896 – 902
Abstract

Hypertrophic cardiomyopathy (HCM) can be classified into at least 4 major anatomic subsets based upon the septal contour, and the location and extent of hypertrophy: reverse curvature-, sigmoidal-, apical-, and neutral contour-HCM. Here, we sought to identify genetic determinants for sigmoidal-HCM and hypothesized that Z-disc HCM may be associated preferentially with a sigmoidal phenotype. Utilizing PCR, DHPLC, and direct DNA sequencing, we performed mutational analysis of five genes encoding cardiomyopathy associated Z-disc proteins. The study cohort consisted of 239 unrelated patients with HCM previously determined to be negative for mutations in the 8 genes associated with myofilament-HCM. Blinded to the Z-disc genotype status, the septal contour was graded qualitatively using standard transthoracic echocardiography. Thirteen of the 239 patients (5.4%) had one of 13 distinct HCM-associated Z-disc mutations involving residues highly conserved across species and absent in 600 reference alleles: LDB3 (6), ACTN2 (3), TCAP (1), CSRP3 (1) and VCL (2). For this subset with Z-disc-associated HCM, the septal contour was sigmoidal in 11 (85%) and apical in 2 (15%). While Z-disc-HCM is uncommon, it is equal in prevalence to thin filament-HCM. In contrast to myofilament HCM, Z-disc HCM is associated preferentially with sigmoidal morphology.

Keywords

Hypertrophy, cardiomyopathy, septum, echocardiography, genes, Z-disc
Introduction

Affecting 1 in 500 persons, hypertrophic cardiomyopathy (HCM) is the most common identifiable cause of sudden death in young athletes and is the most common heritable cardiovascular disease[1]. Characterized by unexplained myocardial hypertrophy in the absence of precipitating factors such as hypertension or aortic stenosis, HCM is underscored by profound genetic and phenotypic heterogeneity. Since the sentinel discovery of mutations involving the $\text{MYH7}$-encoded $\beta$-myosin heavy chain as the pathogenetic basis for HCM in 1990[2], more than 300 mutations scattered among at least 12 HCM-susceptibility genes encoding sarcomeric proteins have been identified.

The first link to be drawn between septal morphologies was a result of a pre-genomics era HCM study by Lever and colleagues where septal contour was found to be age-dependent with a predominance of the sigmoid septum with normal curvature being present in the elderly[3]. This was followed up by an early genotype-phenotype observation by Seidman and colleagues involving a small number of patients and ultimately revealed that patients with mutations in the beta myosin heavy chain (MYH7-HCM) generally had reversed curvature septal contours[4]. Most recently, we discovered that myofilament-HCM may have a predilection for a reverse curvature septal phenotype regardless of age[5]. After analyzing all echocardiograms of 382 previously genotyped and published patients[6, 7, 8], multivariate analysis demonstrated that reverse septal curvature was the only, independent predictor of myofilament HCM with an odds ratio of 21[5]. Moreover, the yield of the commercially available HCM genetic test (panel A and panel B) which examines 8 genes responsible for myofilament-HCM was 79% in reverse curve-HCM but only 8% in sigmoidal-HCM.

These observations provide the rationale for seeking novel genetic determinants that confer susceptibility for sigmoidal-HCM. Recent attention has been focused on proteins outside the cardiac myofilament, involved in the cyto-architecture and cardiac stretch sensor mechanism of the cardiomyocyte. Mutations in three such proteins localized to the cardiac Z-disc, $\text{CSRP3}$-encoded muscle LIM protein (MLP), $\text{TCAP}$-encoded telethonin and $\text{VCL}$-encoded vinculin, including its cardiac specific insert of exon 19 that yields metavinculin, have previously been established as both HCM[9, 10, 11, 12, 13] and dilated cardiomyopathy (DCM)-susceptibility genes[9, 10, 11, 12, 13, 14, 15].
Additionally, it has been recognized that these divergent cardiomyopathic phenotypes of HCM and DCM are partially allelic disorders with ACTC, MYH7, TNNT2, TPM1, MYBPC3, TTN, MLP, TCAP, and VCL established as both HCM- and DCM-susceptibility genes[10, 11, 12, 14, 16, 17, 18, 19, 20].

These observations prompted us to consider perturbations in the cardiac Z-disc as another pathway for hypertrophic or dilated cardiomyopathy. Besides the three aforementioned Z-disc proteins implicated in HCM, we considered two additional genes: ACTN2-encoded alpha-actinin 2 and LDB3-encoded LIM domain binding 3 (official HUGO nomenclature; also known as ZASP-encoded Z-band associated alternatively spliced PDZ-motif protein), as candidates for HCM. Both genes have been implicated in the pathogenesis of DCM and encode proteins that are key binding partners of the previously mentioned HCM-associated, Z-disc proteins[14, 21]. The published Q9R-ACTN2 missense mutation inhibited cellular function and was associated with extra-nuclear localization in cultured cells with co-immunoprecipitation studies showing its failure to bind to MLP[14]. LDB3-associated animal models reveal that null mice completely devoid of this protein lose their ability to maintain structural integrity of the Z-disc, leading to impaired contraction and perinatal death[22].

Because of the specific structure-function relationship of the proteins in the cardiac Z-disc[23, 24] and the specific cardiomyocyte stretch response mechanism of these proteins[25], we hypothesized that Z-disc HCM might be preferentially sigmoidal. We speculate that in the presence of Z-disc mutations, the compensatory hypertrophic response may be greatest in areas of highest stress (i.e. LVOT), thereby resulting in the basal septal bulge and sigmoidal shaped contour.
Methods

Between April 1997 and December 2001, a total of 382 unrelated patients (210 male, mean maximum left ventricular wall thickness (MLVWT) 21.5 ± 6mm) had both comprehensive echocardiographic examination and evaluation in Mayo Clinic’s HCM clinic and genetic testing. HCM was diagnosed according to WHO criteria as unexplained cardiac hypertrophy (>13 mm) in the absence of hypertrophy inciting factors such as aortic stenosis. Following written informed consent for this IRB-approved research protocol, DNA was extracted from the blood samples using Purgene DNA extraction kits (Gentra, Inc., Minneapolis, Minnesota). After a comprehensive analysis of the eight most common myofilament HCM-associated genes, 239 patients (131 male, mean MLVWT 20.7 ± 6mm) remained without a pathogenetic explanation and are in this study referred to as “myofilament genotype negative” [6, 7, 8, 26].

This subset was analyzed for mutations in all translated exons of all published, cardiomyopathy-associated Z-disc genes: CSRP3-encoded muscle LIM protein (MLP), TCAP-encoded telethonin (TCAP), VCL-encoded vinculin, ACTN2-encoded alpha-actinin 2 (ACTN2) and LDB3-encoded LIM domain binding protein 3 (LDB3), using polymerase chain reaction (PCR), denaturing high performance liquid chromatography (DHPLC) (Transgenomic, Omaha NE) and direct DNA sequencing (ABI Prism 377; Applied Biosystem, Foster City, California). Primer sequences and DHPLC-methods are available upon request. To exclude common non-synonymous polymorphisms, we examined 600 ethnically matched reference alleles.

Echocardiography

Septal curvature and cavity contour were evaluated in the long axis view at end-diastole. Sigmoid septal morphology was defined as a generally ovoid left ventricular (LV) cavity with the septum being concave toward the LV with a pronounced basal septal bulge. Reverse curve septal morphology was defined as a predominant mid-septal convexity toward the left ventricular cavity with the cavity itself having an overall crescent shape. Apical variant HCM was defined as a predominant apical distribution of hypertrophy. Neutral septal contour was defined by an overall straight or variable convexity that was neither predominantly convex nor concave toward the LV cavity. Septal contours were assessed by two independent reviewers (JB and SRO) and genotypic data was kept in a database blinded to all clinical and echocardiographic data.
Results

The demographics of the myofilament genotype negative cohort are shown in Table 1. As indicated in the study design exclusion criteria, no mutations in the eight genes underlying myofilament-HCM (beta myosin heavy chain, myosin binding protein C, etc.) were present in this cohort. This cohort consisted of 239 patients (131 male) with an average age at diagnosis of 45.1 years old and a mean MLVWT of 20.7 mm. Fifty-six percent of patients presented with cardiac symptoms, 24% had a family history of HCM in a first degree relative and 16% had a family history of sudden cardiac death. Forty percent of patients underwent surgical myectomy because of refractory symptoms. In comparison, this subset of patients with myofilament genotype negative-HCM are older, have less hypertrophy, and are less likely to have a reverse curvature shaped septum compared to the 143 patients with myofilament-HCM (Table 1) [5, 6, 7, 8, 26].

Table 1: Demographics of Myofilament Genotype Negative HCM Cohort

<table>
<thead>
<tr>
<th></th>
<th>Myofilament Negative (N = 239)</th>
<th>Myofilament Positive (N = 143)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male/female</td>
<td>131/108</td>
<td>79/64</td>
<td>NS</td>
</tr>
<tr>
<td>Age at diagnosis (years)</td>
<td>45.1 ± 19</td>
<td>35.7 ± 17</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>MLVWT (mm)</td>
<td>20.7 ± 6</td>
<td>22.8 ± 7</td>
<td>0.002</td>
</tr>
<tr>
<td>Mean peak LVOT gradient (mmHG)</td>
<td>48.3 ± 42</td>
<td>45.6 ± 42</td>
<td>NS</td>
</tr>
<tr>
<td>Sigmoidal-shaped septal contour</td>
<td>166 (69%)</td>
<td>15 (10%)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Presenting w/ cardiac symptoms (%)</td>
<td>55.7%</td>
<td>55.8%</td>
<td>NS</td>
</tr>
<tr>
<td>Positive family history of HCM*</td>
<td>24%</td>
<td>47%</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Positive family history of SCD*</td>
<td>16%</td>
<td>25%</td>
<td>NS</td>
</tr>
<tr>
<td>Surgical myectomy</td>
<td>95 (40%)</td>
<td>64 (45%)</td>
<td>NS</td>
</tr>
<tr>
<td>Pacemaker</td>
<td>40 (17%)</td>
<td>28 (19%)</td>
<td>NS</td>
</tr>
<tr>
<td>ICD</td>
<td>23 (10%)</td>
<td>37 (25%)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

HCM, hypertrophic cardiomyopathy; LVOT, left ventricular outflow tract; MLVWT, maximum left ventricular wall thickness; SCD, sudden cardiac death; ICD, implantable cardioverter-defibrillator  * In first degree relative
After analysis of all translated exons of LDB3, CSRP3, TCAP, ACTN2 and VCL, 14 mutations in 13 patients (5%) were discovered. Most mutations were missense mutations conserved over species and absent in 600 ethnically matched reference alleles. S196L-LDB3 was identified in two patients. Mutations and their location in the topology of their respective protein are shown in Figure 1. One patient with the Y468S-LDB3 missense mutation also harbored a second Z-disc mutation, a frame-shift mutation (K42 fs/165) in the CSRP3-encoded muscle LIM protein.

Figure 1: Schematic topologies of analyzed genes and the mutations found. The legend behind the gene name directs to the binding domain shown in its partner-protein. For vinculin, the cardiac specific insert that yields metavinculin (exon 19) is shown.
The clinical phenotype of the 13 patients is shown in Table 2. Overall, the average age at diagnosis was 42.9 ± 18 years with seven of the twelve patients being male. The MLVWT is 20.9 ± 9 mm and the LVOT gradient averaged 56.8 ± 49 mmHg. Eight patients (case 1-3, 5, 6, 11-13) underwent surgical septal myectomy because of refractory symptoms. Pathological reports of the surgical specimens show at least two of the three characteristics (cardiomyocyte hypertrophy, endocardial fibrosis and myofibrillar disarray) of HCM in all cases; half of the specimens showed myofibrillar disarray.
<table>
<thead>
<tr>
<th>Case</th>
<th>Gene</th>
<th>Mutation</th>
<th>Sex</th>
<th>Age at Dx (yrs)</th>
<th>MLVWT (mm)</th>
<th>LVOT (mmHg)</th>
<th>Septal shape</th>
<th>Fam Hx of HCM</th>
<th>Fam Hx of SCD</th>
<th>Treatment</th>
<th>Pathology report</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>ACTN2</td>
<td>G111V</td>
<td>M</td>
<td>31.4</td>
<td>20</td>
<td>100</td>
<td>Sigmoid</td>
<td>No</td>
<td>No</td>
<td>Myectomy</td>
<td>Marked myocyte hypertrophy, focal myocyte disarray, endocardial fibrosis</td>
</tr>
<tr>
<td>2</td>
<td>ACTN2</td>
<td>T495M</td>
<td>M</td>
<td>32.5</td>
<td>16</td>
<td>0</td>
<td>Sigmoid</td>
<td>No</td>
<td>No</td>
<td>Myectomy</td>
<td>Marked endocardial fibrosis, myocyte hypertrophy, interstitial fibrosis</td>
</tr>
<tr>
<td>3</td>
<td>ACTN2</td>
<td>R759T</td>
<td>M</td>
<td>17.9</td>
<td>16</td>
<td>120</td>
<td>Sigmoid</td>
<td>No</td>
<td>No</td>
<td>Myectomy</td>
<td>No report</td>
</tr>
<tr>
<td>4</td>
<td>CSRP3</td>
<td>Q91L</td>
<td>M</td>
<td>44.5</td>
<td>22</td>
<td>18</td>
<td>Sigmoid</td>
<td>No</td>
<td>No</td>
<td>Pacemaker</td>
<td>NA</td>
</tr>
<tr>
<td>5</td>
<td>TCAP</td>
<td>R70W</td>
<td>F</td>
<td>44.2</td>
<td>46</td>
<td>19</td>
<td>Sigmoid</td>
<td>Yes</td>
<td>No</td>
<td>Myectomy, Pacemaker</td>
<td>Severe myocyte hypertrophy, moderate interstitial fibrosis</td>
</tr>
<tr>
<td>6</td>
<td>LDB3</td>
<td>S196L</td>
<td>F</td>
<td>73.0</td>
<td>19</td>
<td>64</td>
<td>Sigmoid</td>
<td>No</td>
<td>No</td>
<td>Myectomy</td>
<td>Marked myocyte hypertrophy, moderate endocardial fibrosis, focal myocyte disarray</td>
</tr>
<tr>
<td>7</td>
<td>LDB3</td>
<td>S196L</td>
<td>F</td>
<td>63.8</td>
<td>13</td>
<td>0</td>
<td>Apical</td>
<td>No</td>
<td>No</td>
<td>Rx</td>
<td>NA</td>
</tr>
<tr>
<td>8</td>
<td>LDB3</td>
<td>D366N</td>
<td>M</td>
<td>68.5</td>
<td>18</td>
<td>16</td>
<td>Sigmoid</td>
<td>No</td>
<td>No</td>
<td>Rx</td>
<td>NA</td>
</tr>
<tr>
<td>9</td>
<td>LDB3</td>
<td>Y468S, K42 fs/165</td>
<td>M</td>
<td>46.8</td>
<td>18</td>
<td>112</td>
<td>Sigmoid</td>
<td>No</td>
<td>No</td>
<td>Rx</td>
<td>NA</td>
</tr>
<tr>
<td>10</td>
<td>LDB3</td>
<td>Q519P</td>
<td>F</td>
<td>21.2</td>
<td>15</td>
<td>55</td>
<td>Sigmoid</td>
<td>Yes</td>
<td>No</td>
<td>Rx</td>
<td>NA</td>
</tr>
<tr>
<td>11</td>
<td>LDB3</td>
<td>P615L</td>
<td>M</td>
<td>28.3</td>
<td>27</td>
<td>120</td>
<td>Sigmoid</td>
<td>No</td>
<td>No</td>
<td>Myectomy</td>
<td>Moderate myocyte, mild to moderate focal endocardial fibrosis</td>
</tr>
<tr>
<td>12</td>
<td>VCL</td>
<td>L277M</td>
<td>F</td>
<td>76</td>
<td>20</td>
<td>0</td>
<td>Sigmoid</td>
<td>No</td>
<td>No</td>
<td>Myectomy</td>
<td>Myocyte hypertrophy, cardiomyocyte disarray, interstitial fibrosis</td>
</tr>
<tr>
<td>13</td>
<td>VCL</td>
<td>R975W</td>
<td>F</td>
<td>42.8</td>
<td>22</td>
<td>0</td>
<td>Apical</td>
<td>No</td>
<td>No</td>
<td>Myectomy</td>
<td>Marked myocyte hypertrophy, mild interstitial fibrosis, focal myofibrillar disarray</td>
</tr>
</tbody>
</table>
In contrast to the patients with myofilament-HCM from our previous study, none of the patients with Z-disc HCM exhibited reverse septal curvature echocardiographically (104/143 vs. 0/13, p-value < 0.0001, Figure 2). Instead, 11 of the 13 patients (85%) had a sigmoidal shaped septum and the other 2 patients had apical-HCM (case 7 and 13). For the entire original cohort of 382 unrelated patients, a putative pathogenic explanation for sigmoidal-HCM has increased from 8% (myofilament genotype positive) to now 14% with inclusion of Z-disc mediated disease (Figure 2). The majority of sigmoidal-HCM remains genotypically unexplained.

Figure 2: Overview of the genotype-phenotype relationships between the two most common septal morphologies (bottom) and the presence of mutations in the cardiac Z-disc (top-middle) or the myofilament (top-sides). Arrows pointing towards the morphologies, represent the frequency of that morphology for a particular genotype. Arrows pointing towards the myofilament or Z-disc represent the number of mutations present when showing a particular septal morphology.
Discussion

Due to the hundreds of mutations scattered throughout the genes which encode proteins of the myofilament, HCM has long been considered a disease of the sarcomere, more specifically, a disease of the myofilament. With the recent discovery of HCM associated mutations in genes encoding for proteins of the Z-disc[9, 10, 11, 12, 14] and the distinction whereby HCM associated mutations in \textit{PRKAG2} and \textit{LAMP2} have categorized certain cases of glycogen storage disease[27, 28], the spectrum of genetically-mediated disease pathways continues to expand.

Although specific mutations in particular genes may be rare, the question arises as to whether there may be significant genotype-phenotype correlations associated with distinct HCM-yielding pathways such as myofilament-, Z-disc, or metabolic-HCM. To this end, we further explored our recent discovery that linked reverse curvature HCM with mutations in genes encoding proteins of the myofilament (i.e. myofilament-HCM) [5]. Here, we demonstrated that reverse septal curvature was the strongest, independent predictor of the presence of a myofilament mutation (OR 21, p<0.001) over age and MLVWT[5].

\textbf{The cardiac Z-disc as a novel target in the pathogenesis of HCM}

Focusing on the myofilament negative subgroup, we extended our investigation to encompass five cardiomyopathy-susceptibility genes that encode important and interacting proteins that are key constituents of the cardiac Z-disc architecture. The Z-disc is an intricate assembly of proteins at the Z-line of the cardiomyocyte sarcomere. Extensively reviewed, proteins of the Z-disc are important in the structural and mechanical stability of the sarcomere as they appear to serve as a docking station for transcription factors, Ca$^{2+}$-signaling proteins, kinases and phosphatases[23, 24]. In addition, this assembly of proteins seems to serve as a way station for proteins that regulate transcription by aiding in their controlled translocation between the nucleus and the Z-disc[23, 24].
With all of these roles, a main implication for the Z-disc is its involvement in the cardiomyocyte stretch sensing and response systems [25]. While this is a critical task which is an integral component of Z-disc function in the long term, there is the potential that the Z-disc may transduce multiple signaling pathways during stress, translating into hypertrophic responses, cell growth and remodeling [29]. Based on this potentially important structure-function relationship and its role in the cardiomyocyte stretch response system, we hypothesized that perturbations in the cardiac Z-disc may confer susceptibility for the development of sigmoidal-HCM.

**Z-disc-HCM is preferentially sigmoidal**

Indeed, after extensive analysis of the genes encoding these 5 key Z-disc proteins, we observed a very strong predilection for sigmoidal disease in the presence of a rare mutation that disrupts a Z-disc protein. In fact, in contrast to the 79% likelihood for myofilament-HCM in the setting of reverse curvature-HCM, none of the patients within this subgroup of Z-disc-HCM displayed reverse septal curvature. Although the vast majority of sigmoidal HCM in our cohort still is genetically unexplained, the yield of genetic testing for sigmoidal curvature has nearly doubled by extending the genetic testing from the 8 myofilament-HCM genes that are tested for commercially to include these 5 genes associated with Z-disc-HCM. We speculate that Z-disc HCM leads to a hypertrophic response that is expressed in the areas of highest stress (i.e. LVOT) and therefore predisposes to a sigmoidal septal contour.

These observations generate several intriguing questions regarding HCM in association with a sigmoidal septal contour. Whereas in previous morphologic studies, Lever and colleagues associated sigmoidal-HCM with older age [3], the underlying genotype rather than age appears to be the predominant determinant of septal morphology [5]. Given that the vast majority of our patients with sigmoidal HCM still lack a putative disease-causing mutation, it remains to be determined whether such patients possess, in fact, congenital HCM (i.e. a primary HCM-predisposing genetic mutation). It can be speculated that, especially in the sigmoidal septal subgroup, the sum of all contributors – the presence or absence of a mutation or LVH promoting polymorphisms [30], an unidentified genetic substrate, environmental factors and hypertension – culminates in what is clinically labeled as HCM.
This multi-factorial model for sigmoidal HCM is supported by the significantly older age at diagnosis of patients with sigmoidal HCM (49 years) compared to those with reverse curvature-HCM (32 years)[5]. Furthermore, nearly 20% of patients classified with sigmoidal-HCM were noted to have mild hypertension [5]. Although diagnosed with HCM and presently showing co-existent hypertension, a subset of this group may have a basal septum more sensitive to the pro-hypertrophy trigger of increased afterload, precipitating basal septal hypertrophy (sigmoidal disease), but nonetheless culminating in a clinical diagnosis of HCM. In this scenario, a Mendelian genetic mechanism will not be found.

On the other hand, this novel genotype-phenotype association characterized by predilection for sigmoidal, basal septal hypertrophy in the setting of perturbations in the cardiac Z-disc raises the possibility that other constituents of the Z-disc (> 20 proteins) may host additional HCM-susceptibility mutations in general and sigmoidal-HCM susceptibility mutations in particular. For example, as one of the central proteins of the Z-disc, ACTN2 binds to a large number of proteins, including ALP-encoded actinin-associated LIM-protein [31], CapZ-encoded actin capping protein [32] or S100, of which the S100B-isoform seems to function as an inhibitor of the hypertrophic response [33]. ALP, CAPZ and S100 may represent the next tier of HCM candidate genes to further test our hypothesis that sigmoidal septal shaped HCM is associated with perturbations in the cardiac Z-disc.
Conclusions

Thus far, examination of the five established cardiomyopathy susceptibility genes, encoding key components of the Z-disc, demonstrate that perturbations in the Z-disc is a much less common cause for HCM compared to the two most common HCM-associated genotypes of myosin binding protein C- and beta myosin heavy chain-HCM. Nevertheless, Z-disc HCM is as common as thin filament-HCM (i.e., troponin T-, troponin I-, tropomyosin-, or actin-HCM). However, unlike myofilament HCM, Z-disc HCM is preferentially sigmoidal. Whether a significant proportion of sigmoidal disease will be explained by perturbations in other components of the cardiac Z-disc awaits further investigation.
References


