Inherited Cardiomyopathies: Integrating Genetic Understanding to Clinical Management

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Translational Genomic Medicine in Plain Populations
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Cleveland Clinic
Cardiomyopathy

“Heterogeneous group of diseases of the myocardium associated with mechanical and/or electrical dysfunction that usually (but not invariably) exhibit inappropriate ventricular hypertrophy or dilatation and are due to a variety of causes that frequently are genetic.”

Maron et al, *Circulation* 2006
Genetic Mutations in Cardiomyopathies

Wilde & Behr. Nat Rev Cardiol 2013
### Common Cardiomyopathy Genes

<table>
<thead>
<tr>
<th>Disease</th>
<th>Yield of Test</th>
<th>Common Genes</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Hypertrophic Cardiomyopathy (HCM)</strong></td>
<td>~60%</td>
<td>MYBPC3 (sarcomere)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>MYH7 (sarcomere)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>TNNT2 (sarcomere)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>TPM1 (sarcomere)</td>
</tr>
<tr>
<td><strong>Dilated Cardiomyopathy (DCM)</strong></td>
<td>~35%</td>
<td>TTN (sarcomere)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>MYH7 (sarcomere)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>LMNA (nuclear lamina)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>TNNT2 (sarcomere)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>RBM20 (splicesome)</td>
</tr>
<tr>
<td><strong>Arrhythmogenic Right Ventricular Cardiomyopathy (ARVC)</strong></td>
<td>~50%</td>
<td>PKP2 (desmosome)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>DSG (desmosome)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>DSP (desmosome)</td>
</tr>
</tbody>
</table>

Variable Clinical Presentations of Inherited Cardiomyopathies

Cardiac:
- Left Ventricular Involvement (including myocarditis)
- Right Ventricular Involvement
- Arrhythmias and sudden cardiac death
- Conduction Abnormalities

Non-Cardiac:
- Skeletal Muscle Involvement
- Neuropathy
- Sensorineural Hearing Loss
- Multi-system Involvement
Hypertrophic Cardiomyopathy (HCM)

Prevalence: ~1:500
- ~60% sarcomere gene mutations in 11 protein genes (>400 reported)
- Myocyte hypertrophy and disarray

Natural History: variable
- Intrinsic defect (genetic)
- Septal hypertrophy (puberty)
  - ± diastolic dysfunction
  - ± dynamic / resting outflow obstruction
  - ± microvascular ischemia / fibrosis
  - ± mitral valve abnormalities
- ~20% progressed into refractory heart failure or dilated cardiomyopathy
- Sudden cardiac death
HCM: Discovery, Diagnosis, & Testing

Gross Anatomy & Imaging
- 1958: 1st HCM report (Teare)
- 1962: Familial disease
- 1973: Advent of echo diagnosis (M-mode)
- 1960: First myectomy
- 1964: 1st comprehensive disease description (Braunwald)
- 1979: 2-D echo

Genetics
- 1989: Map HCM to chromosome 14q1
- 1992: Mutations & prognosis MYBPC3
- 2003: Commercial genetic testing
- 2011: ≥10 genes; > 1400 mutations
- 1990: First HCM gene (MYH7)
- 1995: Prevalence (1:500)
- 2000: ICD for SD Prevention
- 2009: 4 testing labs (U.S.)

Maron et al, J Am Coll Cardiol 2012
Gene-Phenotype Heterogeneity in Inherited Cardiomyopathies


Maron B, *Eur Heart J* 2012

Sigmoid

Reverse curve

“Phenocopies” – LAMP2 Mutation (Lysosome-associated membrane protein 2)
Current Approach to Genetic Testing

Patient with unexplained LVH

Family history, genetic counseling & testing

Sarcomere mutation (+)

Storage/metabolic mutation (+)

No mutation/ variant of unknown significance

Family screening

Mutation (+)

Mutation (-)

Appropriate clinical management with disease specific therapy and assess SCD risk

Clinical therapy and further work-up / testing as appropriate

Close follow-up and counseling Preventive therapies (research)

Modified from Ho et al, Circulation 2010
Interpretation of HCM Genetic Testing

Current Integration of Genetic Strategies for Cardiomyopathies

• Diagnostic clarification and confirmation
  - Confirmation or exclusion of specific diagnoses
  - Clarify ambiguous diagnosis or redirect workup, especially in inherited cardiomyopathies

• Therapeutic triage
  - Advanced therapeutics
  - Prophylactic defibrillator considerations
  - Therapy (RNA interference, adeno-associated virus)

• Family Screening and Intervention
  - Identification of preclinical cohort

• (Pharmacogenetics)
  - Drug toxicities or lack of benefit
  - Heart failure therapies
Hypertrophic cardiomyopathy (HCM) is a myocardial disorder characterized by left ventricular (LV) hypertrophy without dilatation and without apparent cause (ie, it occurs in the absence of severe hypertension, aortic stenosis, or other cardiac or systemic diseases that might cause LV hypertrophy). Numerous excellent reviews and consensus documents provide a wealth of additional background. HCM is the leading cause of sudden death in young people and leads to significant disability in survivors. It is caused by mutations in genes that encode components of the sarcomere. Cardiomyocyte and cardiac hypertrophy, myocyte disarray, interstitial and replacement fibrosis, and dysplastic intramyocardial arterioles characterize the pathology of HCM. Clinical manifestations include impaired diastolic function, heart failure, tachyarrhythmia (both atrial and ventricular), and sudden death. At present, there is a lack of understanding of how the mutations in genes encoding sarcomere disease. Herein, we identify research initiatives that we hope will lead to novel therapeutic approaches for patients with HCM.

Epidemiology

The epidemiology of HCM suggests that it is present in ~1 in 500 adults. Because of the delay in phenotypic expression of the disease, HCM is not commonly recognized clinically in young children, but when it is, it is much more frequently recognized in males. This is likely due to greater penetrance in young males. HCM is underdiagnosed clinically in blacks and in women, yet women tend to present with more marked heart failure than men when they are diagnosed later in life. There is no overall difference in mortality, including sudden cardiac death, between men and women, although sudden cardiac death on the athletic field predominantly occurs in men.
Sarcomeric Proteins in Cardiac Myocytes: Post-Translational Modifications

Pfuhl & Gautel, J Muscle Res Cell Motil 2012
**Myosin Binding Protein C3 (MyBPC3)**

- Represents ~200 hypertrophic cardiomyopathy mutations
- Regulatory phosphorylation of the cardiac isoform by cAMP-dependent protein kinase (PKA)

Haploinsufficiency and Calcium Sensitivity contribute to Manifestations of *MYBPC3* Mutations

Van Dijk et al, *Circ* 2009

How do Sacromeric Mutations Cause HCM?

Teekakirikul et al, JCB 2012
Increased Energetic Cost of Cardiac Contraction in Asymptomatic Mutation Carriers

Witjas-Paalberends et al, Cardiovasc Res 2014
Incidence: more than 20 infants in Geauga settlement during last 16 years (1 of 350 births)

Clinical manifestations: presented with heart failure syndrome during the first three weeks of life

Echo: severe HCM

Life span: 3 – 4 months unless they received a heart transplant

Zahka et al, *Heart* 2008

Severe Neonatal Hypertrophic Cardiomyopathy

SNP microarray analysis

- Mapped to chromosome 11p11.2-p11.12
- Associated with MYBPC3 gene
- Splice site of intron 30

N = normal; C = carrier

Xin et al, Am J Hum Genet 2007
MYBPC3 Gene Mutation

Exon 30 …ACCATGg/gagccca… Intron 30

Normal
Homozygote

IVS30+2T>G
Heterozygote

IVS30+2T>G
Homozygote

Xin et al, Am J Hum Genet 2007
Clinical Questionnaire in Heterozygous MYBPC3 Mutation Carriers

Incidence of clinical symptoms found through a simple questionnaire in heterozygous carriers of c.3330 + 2 T>G mutation in the MYBPC3 gene.

<table>
<thead>
<tr>
<th>Symptom</th>
<th>Group A (≤25 years(^a))</th>
<th>Group B (&gt;25 years(^b))</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total subjects surveyed</td>
<td>39</td>
<td>40</td>
</tr>
<tr>
<td>Dizziness or lightheadedness</td>
<td>7.6%</td>
<td>37.5%</td>
</tr>
<tr>
<td>Heart racing or fluttering</td>
<td>5.1%</td>
<td>50.0%</td>
</tr>
<tr>
<td>Skipped heart beat</td>
<td>0.0%</td>
<td>42.5%</td>
</tr>
<tr>
<td>Easily tired</td>
<td>0.0%</td>
<td>45.0%</td>
</tr>
<tr>
<td>Shortness of breath</td>
<td>2.5%</td>
<td>37.5%</td>
</tr>
<tr>
<td>Chest pain</td>
<td>5.1%</td>
<td>40.0%</td>
</tr>
<tr>
<td>Any of the above symptoms</td>
<td>15.3%</td>
<td>85.0%</td>
</tr>
</tbody>
</table>

The incidence of clinical symptom is significantly higher in Group B than in Group A for each symptom or combination (\(p<0.005\) through chi-square test).

Wang and Xin. *Prog Pediatr Cardiol* 2011
Subclinical echocardiographic abnormalities in phenotype-negative carriers of myosin-binding protein C3 gene mutation for hypertrophic cardiomyopathy

Sabe De, MD, Allen G. Borowski, RDCS, Heng Wang, MD, PhD, Leah Nye, CNP, Baozhong Xin, PhD, James D. Thomas, MD, and W. H. Wilson Tang, MD Nova Scotia, Canada; and Cleveland and Middlefield, OH

Background Early diastolic myocardial tissue Doppler velocities have reported to be reduced in mutation-positive patients with hypertrophic cardiomyopathy (HCM) in some studies even in the absence of left ventricular hypertrophy (LVH). Strain is a sensitive tool in detecting early systolic abnormalities in patients with HCM. Our goal is to examine novel echocardiographic characteristics of phenotype-negative carriers for a known sarcomeric gene mutation for HCM.

Methods We evaluated 41 consecutive subjects with a known myosin-binding protein C3 (MYBPC3) mutation (c.3330+2T>G). Subjects who were mutation positive without LVH (G+/LVH-, n = 35) were compared with healthy controls (n = 30) regarding tissue Doppler and segmental longitudinal strain measures.

Results The G+/LVH- group was similar to the healthy controls with respect to chamber size, left ventricular mass index, and most diastolic filling parameters, including tissue Doppler–derived early diastolic annular velocities. Global longitudinal strain was similar for both groups (20.3 ± 2.1 vs 19.8 ± 1.8, P = .36), although regional segment analysis showed a notable reduction in the basal septum (16.8 ± 3.1 vs 19.0 ± 4.0%, P = .02) and increase in the basal posterior (22.5 ± 5.2 vs 17.9 ± 5.2, P = .001) as well as mid posterior (21.8 ± 4.7 vs 18.2 ± 3.0, P = .001) walls.

Conclusions In our cohort of phenotype-negative carriers of a specific MYBPC3 mutation, there were minimal differences in conventional 2-dimensional, Doppler, and speckle-tracking–derived parameters of systolic and diastolic function compared with that of healthy subjects. The presence of regional alterations in strain indicative of the presence of underlying subclinical disease requires further validation. (Am Heart J 2011;162:262-267.e3.)
Echocardiographic Evaluation of Cardiac Structure and Function

Kirkpatrick et al, JACC 2007
Speckle Tracking Technique for Assessing Myocardial Mechanics

Strain:
Myocardial deformation
\[
\frac{L - L_0}{L_0}
\]

Strain Rate:
Rate of contraction or expansion
- How fast is the myocardium shortening or lengthening?

\[ \Rightarrow \text{Peak systolic strain rate correlates with Contractility} \]

Ho, J Cardiovasc Transl Res 2011
Echocardiographic Characteristics of HCM Gene Mutation Carriers

Ho, J Cardiovasc Transl Res 2011
## Echo Cohort Subject Characteristics

<table>
<thead>
<tr>
<th></th>
<th>G+ / LVH- (n=35)</th>
<th>Normal Controls (n=30)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age (years)</strong></td>
<td>30 ± 14</td>
<td>35 ± 12</td>
</tr>
<tr>
<td><strong>Male Gender (%)</strong></td>
<td>51 (18%)</td>
<td>47 (14%)</td>
</tr>
<tr>
<td><strong>Height (cm)</strong></td>
<td>165 ± 13</td>
<td>170 ± 10</td>
</tr>
<tr>
<td><strong>BMI (kg/m²)</strong></td>
<td>24.8 ± 5.9</td>
<td>23.9 ± 3.0</td>
</tr>
<tr>
<td><strong>Systolic BP (mm Hg)</strong></td>
<td>119 ± 10</td>
<td>112 ± 12 *</td>
</tr>
<tr>
<td><strong>Diastolic BP (mm Hg)</strong></td>
<td>73 ± 7</td>
<td>66 ± 7 *</td>
</tr>
<tr>
<td><strong>HR (bpm)</strong></td>
<td>71 ± 12</td>
<td>67 ± 11 *</td>
</tr>
<tr>
<td><strong>LVEF (%)</strong></td>
<td>61 ± 4</td>
<td>58 ± 4 *</td>
</tr>
</tbody>
</table>

* Denotes p<0.01; G+/LVH- = MYBPC3 mutation carriers without LVH

De et al, *Am Heart J* 2012
### Standard Echocardiographic Parameters

<table>
<thead>
<tr>
<th>Parameter</th>
<th>G+/LVH-</th>
<th>Normal Controls</th>
</tr>
</thead>
<tbody>
<tr>
<td>Septum (cm)</td>
<td>$1.0 \pm 0.2$</td>
<td>$0.9 \pm 0.1$</td>
</tr>
<tr>
<td>Posterior Wall (cm)</td>
<td>$0.9 \pm 0.2$</td>
<td>$0.9 \pm 0.1$</td>
</tr>
<tr>
<td>LV mass (g)</td>
<td>$143 \pm 50$</td>
<td>$146 \pm 41$</td>
</tr>
<tr>
<td>LV mass index (g/m²)</td>
<td>$80 \pm 19$</td>
<td>$80 \pm 18$</td>
</tr>
<tr>
<td>MV E (cm/s)</td>
<td>$84 \pm 15$</td>
<td>$77 \pm 13$</td>
</tr>
<tr>
<td>MV A (cm/s)</td>
<td>$58 \pm 18$</td>
<td>$45 \pm 12$</td>
</tr>
<tr>
<td>E/A ratio</td>
<td>$1.6 \pm 0.6$</td>
<td>$1.8 \pm 0.5$</td>
</tr>
<tr>
<td>DT (ms)</td>
<td>$185 \pm 38$</td>
<td>$186 \pm 24$</td>
</tr>
<tr>
<td>PV Adur (cm)</td>
<td>$115 \pm 18$</td>
<td>$105 \pm 17$</td>
</tr>
</tbody>
</table>

* Denotes $p<0.01$; G+/LVH- = *MYBPC3* mutation carriers without LVH

De et al, *Am Heart J* 2012
# Tissue Doppler Imaging Parameters

<table>
<thead>
<tr>
<th></th>
<th>G+/LVH-</th>
<th>Normal Controls</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Mitral Annular Lateral</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sa</td>
<td>10.2 ± 2</td>
<td>9.1 ± 2.1</td>
</tr>
<tr>
<td>Ea</td>
<td>16.4 ± 4.9</td>
<td>14.1 ± 3.0</td>
</tr>
<tr>
<td>Aa</td>
<td>8.8 ± 3.0</td>
<td>8.1 ± 1.4</td>
</tr>
<tr>
<td><strong>Averaged Sa</strong></td>
<td>9.0 ± 1.3</td>
<td>8.5 ± 1.6</td>
</tr>
</tbody>
</table>

|                      |               |                 |
| **Mitral Annular Septal** |             |                 |
| Sa                   | 7.9 ± 1.2     | 8.0 ± 1.6       |
| Ea                   | 11.7 ± 3.2    | 11.0 ± 2.6      |
| Aa                   | 7.5 ± 2.2     | 8.1 ± 1.4       |
| **Averaged Sa**      | 9.0 ± 1.3     | 8.5 ± 1.6       |

* Denotes p<0.01; G+/LVH- = MYBPC3 mutation carriers without LVH

De et al, *Am Heart J* 2012
Regional Longitudinal Strain Patterns

**A** Basal Septum

- p = 0.02

**B** Basal Posterior Wall

- p = 0.002

**C** Mid Posterior Wall

- p = 0.001

G+/LVH- = MYBPC3 mutation carriers without LVH

De et al, *Am Heart J* 2012
Low Plasma BNP in Asymptomatic Carrier DDC Cohort

Tang et al, ACC 2009 (abstract)
## Comparison of Other Cardiac and Inflammatory Biomarkers

<table>
<thead>
<tr>
<th></th>
<th>Homozygous Carriers (n=3)</th>
<th>Heterozygous Carriers (n=55)</th>
<th>Non-Carriers (n=67)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>cTnI (ng/mL)</strong></td>
<td>0.09 ± 0.15</td>
<td>N/D</td>
<td>N/D</td>
</tr>
<tr>
<td><strong>hsCRP (mg/L)</strong></td>
<td>2.1 ± 2.9</td>
<td>1.8 ± 3.4</td>
<td>1.8 ± 2.7</td>
</tr>
<tr>
<td><strong>MPO (pg/mL)</strong></td>
<td>1,832 ± 2,149</td>
<td>236 ± 378</td>
<td>243 ± 509</td>
</tr>
</tbody>
</table>

N/D = not detectable

cTnI = cardiac troponin I
hsCRP = high-sensitivity C-reactive protein
MPO = myeloperoxidase

Tang et al, HFSA 2009 (abstract)
Implications and Future Directions

Echocardiography

• Imaging abnormalities may be more heterogeneous
• Subtle regional longitudinal strain alterations at septum
• Search for environmental influences or other epigenetic determinants may be important

Biomarkers

• First report of biomarker screening in G+/LVH- subjects
  - Standard clinical biomarkers are unable to distinguish carrier versus non-carrier status
• Unclear role of longitudinal screening and other physiologic evaluation despite large proportion with symptoms and subtle EKG changes
Determinants of Reduced Penetrance of Inherited Diseases

Copper et al, Human Genet 2013
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