Genomics in Myocardial and Structural Heart Disease: From Generic to a Personalized Cardiovascular Approach

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Disclosure: CES is a founder and owns shares in Myokardia Inc., a startup company that develops therapeutics targeting the sarcomere
Clinical Genetic Analyses of 7855 Cases Compared to 60,000 ExAC Controls

Genes With Rare Damaging Variants:
Most Often Encode Sarcomere Proteins
Aka: Hypertrophic Cardiomyopathy

Variants Characteristics:
Rare, Found in ≤ 1:10,000 Controls
Protein Damaging: Loss of Function
Deleterious Missense

Pathogenic
Likely Pathogenic
Variants of Uncertain Significance
Found in Controls

Alfares et al Genet Med, 2015
Walsh et al Genet Med, 2016
Histopathologic Impact of LVH Genes

**Force**
- MYH7, MYBPC3
- TNNT2, TNNI3
- MYL3, MYL2
- TPM1, ACTC
- ACTN, MYOZ2

**Metabolism**
- PRKAG2: Glycogen
- GAA (Pompe): Glycogen
- GLA (Fabry): Glycosphingolipids

**Clearance**
- LAMP2: Cellular Debris
- DES: Misfolded Protein
- TTR: Amyloid

[Images of histopathological findings, including autophagic vesicles and glycogen deposits.]
<table>
<thead>
<tr>
<th>Gene</th>
<th>Inheritance</th>
<th>Outcomes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sarcomere Proteins</td>
<td>Dominant</td>
<td>Adolescent or Later Onset</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Atrial Fibrillation in ~25%</td>
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<tr>
<td></td>
<td></td>
<td>Low SCD &amp; HF Risk</td>
</tr>
<tr>
<td>PRKAG2</td>
<td>Dominant</td>
<td>Adolescent Onset</td>
</tr>
<tr>
<td>Disease</td>
<td></td>
<td>Progressive Conduction</td>
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<tr>
<td></td>
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<td>Highest Pacemaker Rates</td>
</tr>
<tr>
<td>LAMP2</td>
<td>X-linked</td>
<td>Childood Onset, Massive LVH, Systemic Disease, VT, VF, Early Death</td>
</tr>
<tr>
<td>GLA</td>
<td>X-linked</td>
<td>Mid-Life Onset; Renal Disease, Progresses to HF (50 yrs) Therapeutic Enzyme</td>
</tr>
</tbody>
</table>
A GLOBAL INITIATIVE

Boston, MA: Brigham and Women's Hospital: n=590
Boston Children's Hospital: n=202

Ann Arbor MI: n=722
University of Michigan

Palo Alto, CA: n=735
Stanford University

New Haven, CT: n=185
Yale University

Rotterdam, Netherlands: n=844
Erasmus Medical Center

Florence, Italy: n=1,569
Referral Centre for Cardiomyopathies

Sao Paulo, Brazil: n=311
University of Sao Paolo

Iceland: n=177

Composite Data: >125,000 Patient-years
Mean follow up: 5.4 ± 6.9 years per patient

More Than 6000 HCM Patient Records
55% with genetic testing

<table>
<thead>
<tr>
<th>Age group</th>
<th>Incidence in US general population (%)</th>
<th>Incidence in HCM patients (%) (US sites)</th>
<th>P-value for difference in risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>20-29</td>
<td>0.09</td>
<td>0.39</td>
<td>&lt; 0.05</td>
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<tr>
<td>30-39</td>
<td>0.13</td>
<td>0.22</td>
<td>0.44</td>
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<tr>
<td>40-49</td>
<td>0.28</td>
<td>0.66</td>
<td>0.09</td>
</tr>
<tr>
<td>50-59</td>
<td>0.61</td>
<td>1.95</td>
<td>&lt; 0.01</td>
</tr>
<tr>
<td>60-69</td>
<td>1.33</td>
<td>3.99</td>
<td>&lt; 0.01</td>
</tr>
</tbody>
</table>
Identify individual differences and specific subgroups from broader populations

**GENETICS: BRINGING MORE PRECISION TO MEDICINE**

- Improve traditional one-size-fits-all to individualized approach
- Best for the *average* patient $\rightarrow$ Best for *this* patient
How Do Sarcomere Gene Mutations Cause Disease?

HCM Pathogenic Variants Predominate in:
- Myosin Binding Protein C: Loss of Function
- β Myosin Heavy Chain: Missense
HCM Myosin Mutations Increase Sarcomere Power

De Bold et al., Am J Physiol 2007

R403Q
R453C

Normalized Function

V_{actin}
F_{max}
ATPase

WT

Spudich, Biophys. J 2014

Percent wild type velocity

HCM ↑velocity → ↑power
HCM ↑force → ↑power

Wild Type
Diastolic Dysfunction Drives Symptoms in HCM

↑ Pulmonary Pressure > Dyspnea
↑ Atrial Pressure > Atrial Stretch
   >> Atrial Fibrillation
   >> Atrial Thrombus
   >> Stroke
↑ Myocardial Ischemia
   >> Heart Failure

Normal
Age 23 years
E’ velocity: 20.1 cm/sec

Preclinical: Mutation+ No LVH
Age 24 years
E’ velocity: 10.5 cm/sec

Overt HCM
Age 35 years
E’ velocity: 5.2 cm/sec

Ho et al., Circulation 2002
Cardiac Cycle: Contraction & Two Phases of Relaxation

Contraction

Disordered Relaxation (DRX)

Super Relaxation (SRX)

X = ATPase Inhibited

Energy Consumption

Do HCM Variants Alter SRX and DRX Interacting Residues?  
(Alamo et al. eLife. 2017)

Variant Analyses in 6112 HCM and 1315 DCM Patients and 33,370 Controls

Analyses in 6112 HCM Patient Analyses:

Myosin:
Pathogenic Variants: 78% alter Interacting Residues (p=5.25e-13)
Likely Path Variants: 44% alter Interacting Residues (p=7.04e-06)

ELC and RLC:
Pathogenic Variants: All alter Interacting Residues

71% HCM Mutations alter Charge of Normal Residue

Analyses in Other Cohorts:
1315 DCM Patients: No enrichment in Interacting Residues (p=0.66)
33,370 Control Subjects: No enrichment in IHM Residues (p=0.23)

HCM Variants Increase Sarcomere Power and Impair Relaxation 
That Together Increase Energy Demands
MYK-461 (Mavacamten): Inhibits Myosin ATPase
Improves HCM Biophysical and Clinical Finding

Green et al, Science 2016

MYK-461

ATP binding
ADP release
Power Stroke
Pi release
Actin binding
ATP hydrolysis

Myofibrils

ATPase Rate (sec⁻¹)

[MYK-461] (µM)

Fractional Shortening (% Basal)

[MYK-461] µM

0.03 0.1 0.3 1 3
MYK-461 (Mavacamten): ↓LVH & Fibrosis in HCM Models

Green et al, Science 2016
MYK-461 (Mavacamten): ↑ Relaxation in Human HCM LV

- NI LV
- HCM LV
- HCM LV + MYK 461 (0.3 μM)
Translating Genetic Insights into Practice and Treatment

Opportunities
Improves Risk Stratification
Targets Healthcare Resources for Patients and Family Members
Enables Mechanistic Discoveries from which New Therapeutic Targets Emerge

Challenges
High Costs (but Falling Fast) & Inconsistent Insurance Coverage
Variant Interpretation Remains Incomplete (VUS)
Disease Modifiers (both Good and Bad) Remain Unknown
Unexpected, Incidental Findings
Knowledge Gaps among Physicians and Patients
Hypertrophic Cardiomyopathy

- Mutations Inform Biophysical Processes by which the Sarcomere Functions throughout Cardiac Cycle
  - ↑Systolic Performance: Direct Motor Function Effects
  - ↓Diastolic Performance
    - ↓SRX:DRX Ratio
    - ↑ATP Consumption

- Sarcomere = Direct Therapeutic Target
  Small Molecules (461) Normalize Biophysical Properties
  Potential to Treat Disorders Beyond HCM

- Still More to Do in HCM:
  Uncover Causes of Mutation-negative Disease
  Recruitment Ongoing:
  Seidman@Genetics.Med.Harvard.Edu
Clinical Team
Carolyn Ho
Neal Lakdawala
Calum MacRae
Allison Cirino
Barbara McDonough

Research Team
James Ware
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Jim Spudich