Examining Prevailing Genotype-Phenotype Correlations in Hypertrophic Cardiomyopathy: Findings from the Sarcomeric Human Cardiomyopathy Registry

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Hypertrophic Cardiomyopathy
Unanswered Questions

- What are the steps leading from genotype to phenotype?
- How does genetic background impact disease?
- Do certain mutations or genes have stereotypical outcomes?
- How can we use fundamental discoveries to transform clinical care?

Limitations:

- Prior experience drawn largely from point/counterpoint case reports or small individual series
- Sparse longitudinal data - natural history not well described
Founding of SHaRe

Sarcomeric Human Cardiomyopathy Registry

Initial funding: Unrestricted Research Grant, MyoKardia, Inc.

• Leverage comprehensive datasets curated by experienced centers to amass a large-scale, collaborative database of genotyped patients
  • Develop precise estimates of risk
  • Determine how genotype impacts disease
  • Advance understanding of how inherited cardiomyopathies develop
  • Set the stage for the development of new, targeted therapies
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
Sao Paulo, Brazil: n=311
University of Sao Paolo
Iceland: n=177
London, UK: n=313
University College London
Rotterdam, Netherlands: n=844
Erasmus Medical Center
Florence, Italy: n=1,569
Referral Centre for Cardiomyopathies

More Than 5,600 HCM Patient Records Uploaded
55% with genetic testing

Data spanning 1963 through Today
>125,000 patient-years
Median follow up 5.6 years per patient [IQR 1.2, 9.3]
Outcome Definitions

• **Composite:** first occurrence of
  – All-cause death
  – Resuscitated cardiac arrest
  – Cardiac transplantation or LVAD implantation
  – Appropriate ICD discharge
  – Atrial fibrillation
  – Stroke
  – LVEF<55%
  – NYHA class III-IV

• **Ventricular Arrhythmic Composite:** first occurrence of
  – Sudden cardiac death
  – Resuscitated cardiac arrest
  – Appropriate ICD therapy

• **Heart Failure Composite:** first occurrence of
  – Cardiac transplantation/LVAD implantation
  – LVEF<55%
  – NYHA III or IV
Baseline Characteristics
Genetic Background
n=2869 with genetic testing

Test results

- Sarc (-), 1165 (40%)
- Sarc (+), 1508 (52%)
- Sarc (2+), 60 (2.1%)
- Sarc (VUS), 196 (6.7%)

Distribution of Genes

- MYBPC3, 64.2%
- MYH7, 26.5%
- TNNT2, 4.1%
- TNNI3, 1.9%
- TPM1, 0.7%
- MYL2, 2.1%
- MYL3, 0.3%
- ACTC1, 0.3%
### Baseline Characteristics: Sarcomere (+) vs Sarcomere (-)

<table>
<thead>
<tr>
<th></th>
<th>Sarcomere (+) n=1508</th>
<th>Sarcomere (-) N=1165</th>
<th>p-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Female, n (%)</td>
<td>596 (40)</td>
<td>396 (34)</td>
<td>0.004</td>
</tr>
<tr>
<td>Age at diagnosis, years, mean (SD)</td>
<td>39.2 (17.7)</td>
<td>49.3 (17.6)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Race, n (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>White</td>
<td>1371 (91)</td>
<td>978 (84)</td>
<td></td>
</tr>
<tr>
<td>Black</td>
<td>13 (1)</td>
<td>21 (2)</td>
<td></td>
</tr>
<tr>
<td>Other</td>
<td>124 (7)</td>
<td>166 (14)</td>
<td></td>
</tr>
<tr>
<td>Family History HCM, n (%)</td>
<td>365 (24)</td>
<td>123 (11)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Family History of SCD, n (%)</td>
<td>234 (15.5)</td>
<td>131 (11.2)</td>
<td>0.001</td>
</tr>
<tr>
<td>Maximal LV Wall Thickness, mm, mean (SD)</td>
<td>19.6 (6.4)</td>
<td>18.4 (5.1)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>LV Ejection Fraction, %, mean (SD)</td>
<td>63.7 (9.4)</td>
<td>65.0 (9.6)</td>
<td>0.002</td>
</tr>
</tbody>
</table>
Outcomes Analyses
Sarcomere mutations are associated with adverse outcomes

No. at risk

<table>
<thead>
<tr>
<th></th>
<th>Sarc(-)</th>
<th>Sarc(+)</th>
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<tbody>
<tr>
<td>1467</td>
<td>1111</td>
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<tr>
<td>1370</td>
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<tr>
<td>22</td>
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</tbody>
</table>

HR for sarc(+) vs. sarc(-)

- Composite outcome: HR 1.5, p-value < 0.0001
- Death: HR 2.0, p-value < 0.0001
- AF: HR 1.7, p-value 0.002
- Stroke: HR 1.6, p-value < 0.0001
- Arrhythmia composite: HR 1.7, p-value 0.002
- HF composite: HR 1.6, p-value < 0.0001
- LVEF < 55%: HR 1.6, p-value < 0.0001
- NYHA III-IV: HR 1.6, p-value < 0.0001

Worse

Sarc (+) Worse
Outcomes vary between sarcomere genes: MYH7 vs MYBPC3 vs thin filament

No. at risk

<table>
<thead>
<tr>
<th></th>
<th>MYH7</th>
<th>MYBPC3</th>
<th>Thin</th>
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<tbody>
<tr>
<td>MYH7</td>
<td>385</td>
<td>945</td>
<td>101</td>
</tr>
<tr>
<td>MYBPC3</td>
<td>354</td>
<td>889</td>
<td>94</td>
</tr>
<tr>
<td>Thin</td>
<td>221</td>
<td>643</td>
<td>70</td>
</tr>
<tr>
<td></td>
<td>58</td>
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</tr>
<tr>
<td></td>
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<td>1</td>
</tr>
</tbody>
</table>

HR 1.72
p<0.0001
(MYH7 vs MYBPC3)

HR 1.39
P=0.032
(thin vs MYBPC3)

HR 1.39
P=NS
(thin vs MYH7)
Patients with variants of unknown significance resemble Sarc(+) more than Sarc (-) patients

<table>
<thead>
<tr>
<th>Age</th>
<th>No. at risk</th>
</tr>
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<tbody>
<tr>
<td></td>
<td>Sarc(+)</td>
</tr>
<tr>
<td>0</td>
<td>1467</td>
</tr>
<tr>
<td>1</td>
<td>1370</td>
</tr>
<tr>
<td>2</td>
<td>953</td>
</tr>
<tr>
<td>3</td>
<td>310</td>
</tr>
<tr>
<td>4</td>
<td>22</td>
</tr>
</tbody>
</table>

HR for sarc(VUS) vs. sarc(-)

- P-value for composite outcome: 0.005
- P-value for death: 0.98
- P-value for AF: 0.01
- P-value for stroke: 0.30
- P-value for arrhythmia composite: 0.02
- P-value for HF composite: 0.06
- P-value for LVEF<55%: 0.13
- P-value for NYHA III-IV: 0.18

Worse

Sarc (-)

Sarc(VUS)
Summary

• Multicenter collaboration is critical for studying uncommon conditions

• Genotype does matter, but large cohorts are required for meaningful interpretation
  – Sarcomere mutations, whether classified pathogenic or of unknown significance, are associated with a greater burden of adverse outcomes
  – Genetic background carries prognostic significance with moderate hazard ratios (1.5-2.0)
  – Family evaluation and consideration of genetic testing should be part of clinical management
  – Genetic diagnosis will be considered when implementing emerging, disease-modifying therapy
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...and thanks to all of our patients

theshareregistry.org  @SHaRe_Registry