Novel Findings from Next Generation Registries

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

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@SHaRe_Registry
Hypertrophic Cardiomyopathy
Unanswered Questions

• How does genotype impact disease?
• Do certain mutations or genes have stereotypical outcomes?
• How can we advance the knowledge base to transform clinical care?

Limitations:
• Prior experience drawn largely from point/counterpoint case reports or small 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 with prospective longitudinal follow up
- Achieve adequate scale to develop more precise estimates of event rates and better predictors of symptom burden and important outcomes
- Incorporate new information to advance knowledge and foster new insights
A Global Initiative

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

Distribution of Genes

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

MYBPC3, 64.2%
MYH7, 26.5%

TNNT2, 4.1%
TNNT3, 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><strong>Female, n (%)</strong></td>
<td>596 (40)</td>
<td>396 (34)</td>
<td>0.004</td>
</tr>
<tr>
<td><strong>Age at diagnosis, years, mean (SD)</strong></td>
<td>39.2 (17.7)</td>
<td>49.3 (17.6)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td><strong>Race, n (%)</strong></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><strong>Family History HCM, n (%)</strong></td>
<td>365 (24)</td>
<td>123 (11)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td><strong>Family History of SCD, n (%)</strong></td>
<td>234 (15.5)</td>
<td>131 (11.2)</td>
<td>0.001</td>
</tr>
<tr>
<td><strong>Maximal LV Wall Thickness, mm, mean (SD)</strong></td>
<td>19.6 (6.4)</td>
<td>18.4 (5.1)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td><strong>LV Ejection Fraction, %, mean (SD)</strong></td>
<td>63.7 (9.4)</td>
<td>65.0 (9.6)</td>
<td>0.002</td>
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</tbody>
</table>
Outcomes Analyses
Sarcomere mutations are associated with adverse outcomes

**Composite outcome**
- HR for sarc(+) vs. sarc(-) = 1.5, p < 0.0001
- HR for sarc(+) vs. sarc(-) = 2.0, p < 0.0001
- HR for sarc(+) vs. sarc(-) = 1.7, p = 0.002

**Death**
- HR for sarc(+) vs. sarc(-) = 1.6, p < 0.0001

**AF**
- HR for sarc(+) vs. sarc(-) = <0.0001

**Stroke**
- HR for sarc(+) vs. sarc(-) = 0.33

**Arrhythmia composite**
- HR for sarc(+) vs. sarc(-) = <0.0001

**HF composite**
- HR for sarc(+) vs. sarc(-) = <0.0001

**LVEF<55%**
- HR for sarc(+) vs. sarc(-) = <0.0001

**NYHA III-IV**
- HR for sarc(+) vs. sarc(-) = 0.066

**No. at risk**
- Sarc(+) 1467 1370 953 310 22
- Sarc(-) 1111 1077 895 447 31

Age

Freedom from composite outcome (%)
Outcomes vary between sarcomere genes: MYH7 vs MYBPC3 vs thin filament

P = 0.032
HR 1.39
(thin vs MYBPC3)

No. at risk

<table>
<thead>
<tr>
<th>Age</th>
<th>MYH7</th>
<th>MYBPC3</th>
<th>Thin</th>
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<tr>
<td>0</td>
<td>385</td>
<td>945</td>
<td>101</td>
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<td>20</td>
<td>354</td>
<td>889</td>
<td>94</td>
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<td>40</td>
<td>221</td>
<td>643</td>
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<td>60</td>
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</tr>
<tr>
<td>80</td>
<td>3</td>
<td>20</td>
<td>1</td>
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</tbody>
</table>
Multiple sarcomere mutations are associated with more severe outcomes

No. at risk
Sarc(+) 1411 1320 924 300 20
Sarc(2+) 57 50 29 10 3

Age

Multiple outcomes vs. sarc(2+)

Composite outcome
Death
AF
Stroke
Arrhythmia composite
HF composite
LVEF < 55%
NYHA III-IV

HR for sarc(2+)

p-value
0.09
0.22
0.87
0.006
<0.0001
0.32
0.27
0.03

HR 4.8

Sarc (+) Worse
Sarc(2+) Worse
Patients with variants of unknown significance resemble Sarc(+) more than Sarc (-) patients.

**Composite outcome**

- Death: HR for sarc(VUS) vs. sarc(-) = 0.005
- AF: 0.98
- Stroke: 0.01
- HR for sarc(VUS) vs. sarc(-)

**Arrhythmia composite**

- HR for sarc(VUS) vs. sarc(-): 0.02

**HF composite**

- LVEF<55%: 0.06
- NYHA III-IV: 0.13

No. at risk

<table>
<thead>
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<th>Sarc(-)</th>
<th>Sarc(VUS)</th>
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<tr>
<td>Sarc(-)</td>
<td>1467</td>
<td>1111</td>
<td>196</td>
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<tr>
<td></td>
<td>1370</td>
<td>1077</td>
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<td></td>
<td>310</td>
<td>447</td>
<td>55</td>
</tr>
<tr>
<td></td>
<td>22</td>
<td>31</td>
<td>4</td>
</tr>
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</table>

**Age**

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<th>Sarc(-)</th>
<th>Sarc(VUS)</th>
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<td>187</td>
<td>139</td>
<td>55</td>
</tr>
<tr>
<td></td>
<td>139</td>
<td>55</td>
<td>4</td>
</tr>
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**Worse**

- Sarc (-) 14
- Sarc(VUS) 15
Limitations

• Data were collected in the context of providing clinical care
• Follow up is not complete for all individuals. Event rates may be underestimated or time to event overestimated
• There is limited power for analyzing rare events and rare patient cohorts
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 higher prevalence 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
  – Emerging, disease-modifying therapies will integrate genetic diagnosis
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...and thanks to all of our patients

theshareregistry.org

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