Iowa ACC FIT Series 05/16/2020:
Other Heritable Cardiomyopathies and
Topics in Cardiovascular Genetics

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Outline

• Mimickers of HCM
• Dilated Cardiomyopathy (DCM)
• Left Ventricular Noncompaction Cardiomyopathy (LVNC)
• Arrhythmogenic Right Ventricular Cardiomyopathy (ARVC)
• Restrictive Cardiomyopathy (RCM)
• Ordering and Interpreting Genetic Tests
• Useful Resources
Mimickers of Hypertrophic Cardiomyopathy (HCM)
Summary of the nomenclature that distinguishes HCM from other genetic diseases associated with LV hypertrophy.

Left Ventricular Hypertrophy

- Sarcomere Mutation*
- Without Extracardiac or Metabolic Findings + Genetic Substrate Unresolved
- With Extracardiac or Metabolic Findings Associated With or Without Mutant Gene

Hypertrophic Cardiomyopathy

Syndrome† With Left Ventricular Hypertrophy

et al. Circulation 2011;124:2761-2796
<table>
<thead>
<tr>
<th>Gene</th>
<th>Locus</th>
<th>Protein</th>
<th>Syndrome</th>
</tr>
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<tbody>
<tr>
<td>TAZ</td>
<td>Xq28</td>
<td>Tafazzin (G4.5)</td>
<td>Barth syndrome/LVNC</td>
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<tr>
<td>DTNA</td>
<td>18q12</td>
<td>Alpha-dystrobrevin</td>
<td>Barth syndrome/LVNC</td>
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<td>PRKAG2</td>
<td>7q35–q36.36</td>
<td>AMP-activated protein kinase</td>
<td>WPW/HCM</td>
</tr>
<tr>
<td>LAMP2</td>
<td>Xq24</td>
<td>Lysosome-associated membrane protein 2</td>
<td>Danon’s syndrome/WPW</td>
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<tr>
<td>GAA</td>
<td>17q25.2–q25.3</td>
<td>Alpha-1,4-glucosidase deficiency</td>
<td>Pompe’s disease</td>
</tr>
<tr>
<td>GLA</td>
<td>Xq22</td>
<td>Alpha-galactosidase A</td>
<td>Fabry’s disease</td>
</tr>
<tr>
<td>AGL</td>
<td>1p21</td>
<td>Amylo-1,6-glucosidase</td>
<td>Forbes disease</td>
</tr>
<tr>
<td>FXN</td>
<td>9q13</td>
<td>Frataxin</td>
<td>Friedrich’s ataxia</td>
</tr>
<tr>
<td>PTPN11</td>
<td>12q24.1</td>
<td>Protein tyrosine phosphatase, nonreceptor type 11, SHP-2</td>
<td>Noonan’s syndrome, LEOPARD syndrome</td>
</tr>
<tr>
<td>RAF1</td>
<td>3p25</td>
<td>V-RAF-1 murine leukemia viral oncogene homolog 1</td>
<td>Noonan’s syndrome, LEOPARD syndrome</td>
</tr>
<tr>
<td>KRAS</td>
<td>12p12.1</td>
<td>v-Ki-ras2 Kirsten rat sarcoma viral oncogene homolog</td>
<td>Noonan’s syndrome</td>
</tr>
<tr>
<td>SOS1</td>
<td>2p22-p21</td>
<td>Son of sevenless homolog 1</td>
<td>Noonan’s syndrome</td>
</tr>
</tbody>
</table>
Phenocopies of Hypertrophic Cardiomyopathy: Storage Cardiomyopathies

- AMP-Activated Protein Kinase γ2 Subunit (*PRKAG2*)
- Lysosome-Associated Membrane Protein (*LAMP2*): Danon Disease (X-linked)
- α-1,4 glucosidase (*GAA*): Pompe Disease
- α-galactosidase A (*GLA*): Fabry disease (X-linked)

WPW and Other Unusual Features in an “HCM” Family

Table 1. Clinical Characteristics of Affected Individuals in Family AS

<table>
<thead>
<tr>
<th>ID Number</th>
<th>Age/ Sex</th>
<th>EKG</th>
<th>Preexcitation</th>
<th>LVWT</th>
<th>Holter</th>
<th>Clinical</th>
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<tbody>
<tr>
<td>III-1</td>
<td>52/F</td>
<td>PR, LVH</td>
<td>ND</td>
<td>14</td>
<td>CHB(V)</td>
<td>C, P, D, S</td>
</tr>
<tr>
<td>III-3</td>
<td>58/F</td>
<td>LBBB</td>
<td>Adenosine/IR</td>
<td>26</td>
<td>SB, PAF(V)</td>
<td>C, P, D, M</td>
</tr>
<tr>
<td>III-5</td>
<td>50/M</td>
<td>LVH</td>
<td>Adenosine/IR</td>
<td>20</td>
<td>SB, PAF</td>
<td>C, P, D, S, M</td>
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<tr>
<td>III-7</td>
<td>47/M</td>
<td>LBBB</td>
<td>Adenosine/IR</td>
<td>19</td>
<td>PAF, CHB(V)</td>
<td>D, P, S</td>
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<tr>
<td>III-8</td>
<td>47/M</td>
<td>LBBB</td>
<td>Adenosine/IR</td>
<td>11</td>
<td>SB</td>
<td>P, D</td>
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<tr>
<td>III-13</td>
<td>35/F</td>
<td>PR</td>
<td>Adenosine/+</td>
<td>12</td>
<td>N</td>
<td>C, P, D, M</td>
</tr>
<tr>
<td>III-16</td>
<td>41/F</td>
<td>LVH</td>
<td>ND</td>
<td>30</td>
<td>PAF</td>
<td>C, P</td>
</tr>
<tr>
<td>III-18</td>
<td>40/F</td>
<td>PR, LVH</td>
<td>ND</td>
<td>35</td>
<td>N</td>
<td>C, S</td>
</tr>
<tr>
<td>III-19</td>
<td>39/M</td>
<td>LVH</td>
<td>ND</td>
<td>30</td>
<td>N</td>
<td>C, S</td>
</tr>
<tr>
<td>III-22</td>
<td>32/M</td>
<td>LBBB</td>
<td>ND</td>
<td>N/A</td>
<td>N</td>
<td>SCD</td>
</tr>
<tr>
<td>III-24</td>
<td>36/M</td>
<td>LVH</td>
<td>ND</td>
<td>15</td>
<td>SB</td>
<td>C, P, S</td>
</tr>
<tr>
<td>III-25</td>
<td>31/M</td>
<td>LBBB</td>
<td>Adenosine/+</td>
<td>15</td>
<td>SB</td>
<td>C, P, M</td>
</tr>
<tr>
<td>III-26</td>
<td>33/F</td>
<td>LBBB</td>
<td>Adenosine/IR</td>
<td>20</td>
<td>SB</td>
<td>C, D, M</td>
</tr>
<tr>
<td>III-27</td>
<td>37/F</td>
<td>LBBB</td>
<td>+</td>
<td>34</td>
<td>PAF</td>
<td>C, P, D</td>
</tr>
<tr>
<td>III-30</td>
<td>31/M</td>
<td>LVH</td>
<td>Adenosine/IR</td>
<td>13</td>
<td>SB</td>
<td>P, D, M</td>
</tr>
<tr>
<td>IV-2</td>
<td>23/M</td>
<td>PR, LVH</td>
<td>+</td>
<td>25</td>
<td>PAF</td>
<td>C</td>
</tr>
<tr>
<td>IV-3</td>
<td>22/F</td>
<td>LVH</td>
<td>Adenosine/IR</td>
<td>10</td>
<td>N</td>
<td>C</td>
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<tr>
<td>IV-4</td>
<td>12/M</td>
<td>LVH</td>
<td>ND</td>
<td>15</td>
<td>N</td>
<td>C, P, S</td>
</tr>
<tr>
<td>IV-5</td>
<td>20/M</td>
<td>LVH</td>
<td>ND</td>
<td>10</td>
<td>N</td>
<td>C</td>
</tr>
<tr>
<td>IV-6</td>
<td>19/F</td>
<td>N</td>
<td>Adenosine/-</td>
<td>14</td>
<td>N</td>
<td>P, D, S</td>
</tr>
<tr>
<td>IV-7</td>
<td>17/F</td>
<td>LBBB</td>
<td>ND</td>
<td>10</td>
<td>N</td>
<td>D</td>
</tr>
<tr>
<td>IV-9</td>
<td>18/F</td>
<td>LVH</td>
<td>ND</td>
<td>14</td>
<td>N</td>
<td>A</td>
</tr>
<tr>
<td>IV-10</td>
<td>12/M</td>
<td>PR, LVH</td>
<td>ND</td>
<td>15</td>
<td>N</td>
<td>A</td>
</tr>
<tr>
<td>IV-11</td>
<td>18/M</td>
<td>LVH</td>
<td>ND</td>
<td>45</td>
<td>N</td>
<td>C</td>
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<tr>
<td>IV-12</td>
<td>19/F</td>
<td>LBBB</td>
<td>Adenosine/-</td>
<td>18</td>
<td>N</td>
<td>C</td>
</tr>
</tbody>
</table>

EKG, electrocardiogram; PR, short PR < 100 ms; LVH, voltage criteria for left ventricular hypertrophy; LBBB, left bundle branch block; ND, not done; IR, indeterminate response; LVWT, maximum left ventricular wall thickness; N/A, not available; CHB, complete atrioventricular block; SB, sinus bradycardia; PAF, paroxysmal atrial fibrillation; V, permanent pacemaker inserted; C, chest pain; D, dyspnea; M, skeletal muscle pain after exertion; P, palpitations; S, syncope; A, asymptomatic.

AMPK in energy homeostasis

Exercise
Hypoxia

ATP
ADP

Other stimuli,
PKCζ

AMP

CaMKKβ

AMPKK
(LKB1)

AMPK α
AMPK β

GS
(Glycogen synthase)

GLUT4
(Glucose transporter 4)

PFK
(Phosphofructokinase)

eNOS
(Nitric oxide synthase)

IRS1
(Insulin Receptor substrate 1)

TSC1/2

Rheb

mTOR

CFTR

MCD
(Malonyl-CoA carboxylase)

GPAT
(Glycerol-3-phosphate acyltransferase)

ACC2
(Acetyl-CoA carboxylase)

PGC-1α
(PPARγ coactivator)

Leptin

Adiponectin

PPARγ

Glucose uptake and metabolism

Protein synthesis and growth

Triglycerides and Malonyl-CoA

Gene expression
“Metabolic Remodeling” in *PRKAG2* Cardiomyopathy

Inordinate AMPK activity due to mutation of the γ2 subunit

- Fatty acid oxidation ↑
- Glucose entry ↑↑
  - G-6-P ↑↑
  - G-1-P
  - UDPG-PPL ↑↑
  - UDPG
  - GS/GS-p
  - Glycogen ↑↑

*PRKAG2* mutations cause glycogen storage cardiomyopathy, not HCM.

The annulus fibrosis is disrupted in $\gamma$2TG$^{N488I}$ mice, leading to ventricular preexcitation.

Dilated Cardiomyopathy (DCM)
Dilated Cardiomyopathy

- Incidence 5-8/100,000
- Prevalence 36.5/100,000
- 1-year mortality 25% once symptomatic
### Known DCM disease genes explain ~37% of cases.

<table>
<thead>
<tr>
<th>Gene</th>
<th>Protein</th>
<th>Frequency, Familial</th>
<th>Frequency, Sporadic</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Autosomal Dominant Familial Dilated Cardiomyopathy</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ACTC</td>
<td>Cardiac actin</td>
<td>rare</td>
<td>rare</td>
</tr>
<tr>
<td>DES</td>
<td>Desmin</td>
<td>?</td>
<td>?</td>
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<tr>
<td>LMNA</td>
<td>Lamin A/C</td>
<td>7.30%</td>
<td>3.00%</td>
</tr>
<tr>
<td>SGCD</td>
<td>δ-sarcoglycan</td>
<td>rare</td>
<td>rare</td>
</tr>
<tr>
<td>MYH7</td>
<td>β-myosin heavy chain</td>
<td>6.30%</td>
<td>3.20%</td>
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<tr>
<td>TNNT2</td>
<td>Cardiac troponin T</td>
<td>2.90%</td>
<td>1.60%</td>
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<tr>
<td>TPM1</td>
<td>α-tropomyosin</td>
<td>rare</td>
<td>rare</td>
</tr>
<tr>
<td>TTN</td>
<td>Titin</td>
<td>25%</td>
<td>18%</td>
</tr>
<tr>
<td>VCL</td>
<td>Metavinculin</td>
<td>rare</td>
<td>rare</td>
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<tr>
<td>MYBPC3</td>
<td>Myosin-binding protein C</td>
<td>?</td>
<td>?</td>
</tr>
<tr>
<td>CSRP3</td>
<td>Muscle LIM protein</td>
<td>rare</td>
<td>rare</td>
</tr>
<tr>
<td>ACTN2</td>
<td>α-actinin-2</td>
<td>?</td>
<td>?</td>
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<tr>
<td>PLN</td>
<td>Phospholamban</td>
<td>rare</td>
<td>rare</td>
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<tr>
<td>ZASP/LDB3</td>
<td>Cypher/LIM binding domain 3</td>
<td>?</td>
<td>?</td>
</tr>
<tr>
<td>MYH6</td>
<td>α-myosin heavy chain</td>
<td>?</td>
<td>?</td>
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<tr>
<td>ABCC9</td>
<td>SUR2A</td>
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<td></td>
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<tr>
<td>TNNC1</td>
<td>Cardiac troponin C</td>
<td>?</td>
<td>?</td>
</tr>
<tr>
<td>TCAP</td>
<td>Titin-cap or telethonin</td>
<td>rare</td>
<td>rare</td>
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<tr>
<td>SCN5A</td>
<td>Sodium channel</td>
<td>?</td>
<td>?</td>
</tr>
<tr>
<td>EYA4</td>
<td>Eyes-absent 4</td>
<td>?</td>
<td>?</td>
</tr>
<tr>
<td>PSEN1</td>
<td>Presenilin 1 / 2</td>
<td>?</td>
<td>?</td>
</tr>
<tr>
<td>RBM20</td>
<td>Presenilin 1 / 2</td>
<td>3%?</td>
<td>3%?</td>
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<td><strong>X-linked Familial Dilated Cardiomyopathy</strong></td>
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<tr>
<td>DMD</td>
<td>Dystrophin</td>
<td></td>
<td></td>
</tr>
<tr>
<td>TAZ/G4.5</td>
<td>Tafazzin</td>
<td></td>
<td></td>
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<td><strong>Autosomal Recessive Familial Dilated Cardiomyopathy</strong></td>
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<tr>
<td>TNNI3</td>
<td>Cardiac troponin I</td>
<td>?</td>
<td>?</td>
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</table>

Herman DS, et al.  
Known DCM disease genes explain ~37% of cases.
Mechanisms of DCM: Hypotheses

Desmin
Actin
β-sarcoglycan
Dystrophin
Metavinculin

α-tropomyosin
β-myosin heavy chain
Troponin C
Troponin T

Lamin A/C
Thymopoietin

Cardiac muscle LIM protein
Telethonin
Titin

Phospholamban

impaired force transmission
impaired force generation
changes in nuclear structure and function
changes in stretch sensor machinery
Ca\(^{2+}\) regulation

DILATED CARDIOMYOPATHY
### Distinct Mechanisms Leading to HCM and DCM

<table>
<thead>
<tr>
<th></th>
<th>HCM</th>
<th>DCM</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ca(^{2+}) Sensitivity</td>
<td>↑↑</td>
<td>↓</td>
</tr>
<tr>
<td>ATPase Activity</td>
<td>↑↑</td>
<td>↓</td>
</tr>
<tr>
<td>Filament Velocity</td>
<td>↑↑</td>
<td>↓</td>
</tr>
<tr>
<td>Force Generation</td>
<td>↑↑</td>
<td>↓</td>
</tr>
</tbody>
</table>
Fig. 3. TTNtv and survival in DCM. Outcomes in unselected DCM patients with (red) and without (blue) TTNtv.

Angharad M. Roberts et al., Sci Transl Med 2015;7:270ra6

Published by AAAS
Fig. 1. Distribution of TTNtv in healthy individuals and DCM patients, and TTN exon usage in the heart.

Angharad M. Roberts et al., Sci Transl Med 2015;7:270ra6

Published by AAAS
Fig. 2. Factors that discriminate TTNtv in health and disease.
Management of Dilated Cardiomyopathy (DCM)

- Follow ACC/AHA/HFSA Guidelines for the Management of Heart Failure
- Implantable cardioverter defibrillators (ICDs)
  - Standard indications for primary and secondary prevention of SCD
    - NYHA class II and III symptoms, LVEF ≤ 35%
    - SCN5A, LMNA, DES, FLNC variants higher risk
Left Ventricular Noncompaction (LVNC)

- Third most common pediatric cardiomyopathy
- Deep trabeculations
- Poor systolic function with or without dilation
- Mutations in sarcomere and cytoskeletal genes:
  - Alpha actin (*ACTC1*)
  - Alpha actinin 2 (*ACTN2*)
  - α-dystrobrevin (*DTNA*)
  - LIM domain binding 3 (*LDB3*)
  - Cardiac myosin binding protein C (*MYBPC3*)
  - β-myosin heavy chain (*MYH7*)
  - Tafazzin (*TAZ*)
  - Cardiac troponin T (*TNNT2*)

Left Ventricular Noncompaction (LVNC)

Left Ventricular Noncompaction (LVNC)

- Increased risk for LV dilation and CHF
- Possible increased risk for SCD
- Current recommendations suggest no competitive athletics
Anticoagulation in LVNC

• Thromboembolic events occur in 13-24%
• Oral anticoagulation
  - Prior thromboembolism
  - Atrial fibrillation
  - LVEF ≤ 40%
Arrhythmogenic Right Ventricular Cardiomyopathy (ARVC)
Clinical Features of Arrhythmogenic Right Ventricular Cardiomyopathy (ARVC)

• Prevalence ranges from 1/10,000 to 5/10,000
• Inherited disease, typically autosomal dominant
• Progressive replacement of right ventricular myocardium by adipose and fibrous tissue
• Life-threatening ventricular arrhythmias
• Accounts for 20 - 26% of all sudden deaths in the young
• Clinical findings are nonspecific
• Initial pathological changes may be restricted to the right ventricle, but biventricular and left ventricular patterns occur
## Table 1 | Genes associated with AC

<table>
<thead>
<tr>
<th>Reference</th>
<th>Gene</th>
<th>Chromosome locus</th>
<th>Protein</th>
<th>Mode of Inheritance</th>
<th>Comment</th>
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<tbody>
<tr>
<td><strong>Desmosomal genes</strong></td>
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</tr>
<tr>
<td>McKoy et al.(^{31})</td>
<td>JUP</td>
<td>17q21</td>
<td>Junction plakoglobin</td>
<td>AR(^{*})</td>
<td>Cardiocutaneous syndrome</td>
</tr>
<tr>
<td>Asimaki et al.(^{41})</td>
<td>JUP</td>
<td>17q21</td>
<td>Junction plakoglobin</td>
<td>AD</td>
<td>None</td>
</tr>
<tr>
<td>Norgett et al.(^{33})</td>
<td>DSP</td>
<td>6p24</td>
<td>Desmoplakin</td>
<td>AR(^{4})</td>
<td>Cardiocutaneous syndrome</td>
</tr>
<tr>
<td>Rampazzo et al.(^{36})</td>
<td>DSP</td>
<td>6p24</td>
<td>Desmoplakin</td>
<td>AD</td>
<td>None</td>
</tr>
<tr>
<td>Gerull et al.(^{38})</td>
<td>PKP2</td>
<td>12p11</td>
<td>Plakophilin-2</td>
<td>AD, AR</td>
<td>None</td>
</tr>
<tr>
<td>Pilichou et al.(^{39})</td>
<td>DSG2</td>
<td>18q12</td>
<td>Desmoglein-2</td>
<td>AD</td>
<td>None</td>
</tr>
<tr>
<td>Syrris et al.(^{40})</td>
<td>DSC2</td>
<td>18q12</td>
<td>Desmocollin-2</td>
<td>AD, AR</td>
<td>None</td>
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<tr>
<td><strong>Extradesmosomal genes</strong></td>
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<tr>
<td>Tiso et al.(^{44})</td>
<td>RYR2</td>
<td>1q42–q43</td>
<td>Ryanodine receptor 2</td>
<td>AD</td>
<td>CPVT (AC phenocopy)</td>
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<tr>
<td>Beffagna et al.(^{45})</td>
<td>TGFB3</td>
<td>14q23–q24</td>
<td>Transforming growth factor (\beta_3)</td>
<td>AD</td>
<td>Pathogenic or modifier?</td>
</tr>
<tr>
<td>Mener et al.(^{46})</td>
<td>TMEM43</td>
<td>3p25</td>
<td>Transmembrane protein 43 (protein LUMA)</td>
<td>AD</td>
<td>None</td>
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<tr>
<td>van Tintelen et al.(^{47})</td>
<td>DES</td>
<td>2q35</td>
<td>Desmin</td>
<td>AD</td>
<td>Overlap syndrome (DC and HC phenotype, early conduction disease)</td>
</tr>
<tr>
<td>Taylor et al.(^{48})</td>
<td>TTN</td>
<td>2q31</td>
<td>Titin</td>
<td>AD</td>
<td>Overlap syndrome (early conduction disease, AF)</td>
</tr>
</tbody>
</table>

\(^*\) Naxos disease. \(^{\ast}\) Carvajal disease. Abbreviations: AC, arrhythmogenic cardiomyopathy; AD, autosomal dominant; AF, atrial fibrillation; AR, autosomal recessive; CPVT, catecholaminergic polymorphic ventricular tachycardia; DC, dilated cardiomyopathy; HC, hypertrophic cardiomyopathy.
The Cardiac Desmosome

Marcus F I et al. Circulation 2010;121:1533-1541
Genetic Complexity of ARVC

• Gene-dose effects: autosomal recessive forms have more severe phenotype
• Compound heterozygous mutations
• Digenic mutations

Hypothetical Intracellular Desmosome Crosstalk

Management of ARVC

• Follow ACC/AHA/HFSA Guidelines for the Management of Heart Failure

• Implantable cardioverter defibrillator (ICD)
  - Class I for >10% annual SCD risk
    - History of SCA
    - RVFAC ≤ 17%
    - LVEF ≤ 35%
  - Class IIA
    - Syncope
    - NSVT
    - RVFAC 17–24%
    - LVEF 36-45%

• Beta blockers, sotalol, flecainide, amiodarone

• Avoid intense exercise
Online ARVC Risk Calculator

https://arvcrisk.com
Restrictive Cardiomyopathy (RCM)
### Genes Associated with RCM

<table>
<thead>
<tr>
<th>Pathophysiology / Disease</th>
<th>Genes</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Infiltrative</strong></td>
<td></td>
</tr>
<tr>
<td>Amyloidosis</td>
<td>TTR, APOA1</td>
</tr>
<tr>
<td>Primary hyperoxaluria</td>
<td>AGXT (type 1), GRHPR (type 2), HOGA1 (type 3)</td>
</tr>
<tr>
<td><strong>Storage diseases</strong></td>
<td></td>
</tr>
<tr>
<td>Fabry disease</td>
<td>GLA</td>
</tr>
<tr>
<td>Gaucher disease</td>
<td>GBA</td>
</tr>
<tr>
<td>Hereditary hemochromatosis</td>
<td>HAMP, HFE, HFE2, HJV, PNPLA3, SLC40A1, TFR2</td>
</tr>
<tr>
<td>Glycogen storage disease</td>
<td></td>
</tr>
<tr>
<td>Mucopolysaccharidosis type I (Hurler syndrome)</td>
<td>IDUA</td>
</tr>
<tr>
<td>Mucopolysaccharidosis type II (Hunter syndrome)</td>
<td>IDS</td>
</tr>
<tr>
<td>Niemann–Pick disease</td>
<td>NPC1, NPC2, SMPD1</td>
</tr>
<tr>
<td><strong>Noninfiltrative</strong></td>
<td></td>
</tr>
<tr>
<td>Myofibrillar myopathies</td>
<td>BAG3, CRYAB, DES, DNAJB6, FHL1, FLNC, LDB3, MYOT</td>
</tr>
<tr>
<td>Pseuxanthoma elasticum</td>
<td>ABCC6</td>
</tr>
<tr>
<td>Sarcomeric protein disorders</td>
<td>ACTC, MYH7, TNNT2, TNNI3, TNNC1, DES, MYL3, CRYAB</td>
</tr>
<tr>
<td>Werner’s syndrome</td>
<td>WRN</td>
</tr>
<tr>
<td><strong>Endomyocardial</strong></td>
<td></td>
</tr>
<tr>
<td>Endocardial fibroelastosis</td>
<td>BMP5, BMP7, TAZ</td>
</tr>
</tbody>
</table>
Cardiac Amyloidosis

Ali M Agha et al. Open Heart 2018;5:e000881
Management of RCM

- Specific treatment depending on etiology
  - e.g. tafamidis for transthyretin amyloidosis
- Cautious diuresis
- Beta blockers, but not as aggressive as DCM
- Cardiac transplantation
Inherited Cardiomyopathies

- HCM: Force generation and transmission
- Storage cardiomyopathies: Metabolic
- ARVC: Cell-cell adhesion
- DCM: Mixed bag
Principles of Molecular Genetic Testing for Cardiomyopathies
Utility of Genetic Testing

- Identification of presymptomatic family members
  - Enrolment of patients in clinical trials
  - Lifestyle changes, e.g. exercise
- Peace of mind and elimination of need for serial clinical evaluations in genotype-negative patients
- Prognostication and guidance of patient treatment
- Patients with GLA mutations (Fabry disease) can be treated with enzyme replacement
- Guidance of reproductive choices
- Uncertain diagnosis (mild abnormalities on imaging, no family history)
Age Related Penetrance of HCM

Clinical Diagnosis

Gene-based Diagnosis

Ages:
20 19 18 17 15 12 8 15 11 3 8 7 4 3 2
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Contribution of GLA Variants to Cardiac Hypertrophy

<table>
<thead>
<tr>
<th>Gene</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>MYBPC3</td>
<td>46.3%</td>
</tr>
<tr>
<td>MYH7</td>
<td>32.9%</td>
</tr>
<tr>
<td>TNNI3</td>
<td>5.8%</td>
</tr>
<tr>
<td>TNNT2</td>
<td>5.2%</td>
</tr>
<tr>
<td>TPM1</td>
<td>2.6%</td>
</tr>
<tr>
<td>MYL2</td>
<td>2.6%</td>
</tr>
<tr>
<td>MYL3</td>
<td>1.5%</td>
</tr>
<tr>
<td>ACTC</td>
<td>0.5%</td>
</tr>
<tr>
<td>PRKAG2</td>
<td>0.6%</td>
</tr>
<tr>
<td>LAMP2</td>
<td>0.3%</td>
</tr>
<tr>
<td>GLA</td>
<td>1.7%</td>
</tr>
</tbody>
</table>

Enzyme replacement therapy available
Utility of Genetic Testing

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Diagnostic Yield of Genetic Testing

- HCM 51%
  - Familial 65%
  - Sporadic 38%
- Fabry Disease 100%
- DCM ~37%
- ARVC ~30-50%
- Other Cardiomyopathies: Unknown
Genetic Testing Strategy

• Mutation search: Affected individual ~$3000
  – Pathogenic mutation ➔ Cascade screening
  – No mutation found ➔ Not useful
  – Variant of uncertain significance ➔ ? Causal

• Targeted: Cascade screening of relatives, ~$250
  – If pathogenic mutation is known or suspected
  – March sequentially through pedigree
• A relative without symptoms but with a positive result must continue to be evaluated at regular intervals.

• A relative without symptoms and with a negative result is not at elevated risk for developing a cardiomyopathy.
In someone with a clinical diagnosis of disease, a negative result means:

- The clinical diagnosis of disease is incorrect.
- The clinical diagnosis of disease is correct, but:
  - The testing methodology has technical limitations.
  - There are variants outside the “coding” part of the gene that are biologically important.
  - The gene containing the mutation was not analyzed.
  - There are other, currently unidentified genes that are associated with this disease.
Newer and Evolving Genetic Tests

• Disease-specific panels
• Whole exome sequencing (WES)
• Whole genome sequencing (WGS)
Variant of Uncertain Significance

- Is the variant present in other affected family members?
- Is the variant present in normal individuals?
- Is the variant in the same parts of the gene as previously identified mutations?
- Computer modeling
Problems with Genetic Testing

- Cost; variable coverage by insurance
- Test is not useful if mutation is not found
- Treating asymptomatic individuals mostly not proven
- Damage to careers, insurability
- Conclusions may be wrong
SPECIAL ARTICLE

Genetic Misdiagnoses and the Potential for Health Disparities

Arjun K. Manrai, Ph.D., Birgit H. Funke, Ph.D., Heidi L. Rehm, Ph.D., Morten S. Olesen, Ph.D., Bradley A. Maron, M.D., Peter Szolovits, Ph.D., David M. Margulies, M.D., Joseph Loscalzo, M.D., Ph.D., and Isaac S. Kohane, M.D., Ph.D.
Genetic Information Nondiscrimination Act (GINA) of 2008

- Prohibits discrimination by health insurance carriers and most employers on the basis of genetic information.
- Non-discrimination protections do not extend to life insurance, disability insurance, and long-term care insurance.
## Intervals for Clinical Screening

<table>
<thead>
<tr>
<th>Cardiomyopathy</th>
<th>Interval if genetic testing is negative and/or if clinical family screening is negative</th>
<th>Screening interval if a pathogenic variant is present</th>
</tr>
</thead>
<tbody>
<tr>
<td>DCM</td>
<td>Every 3–5 years beginning in childhood</td>
<td>Yearly in childhood; every 1–3 years in adults.</td>
</tr>
<tr>
<td>ARVD/C</td>
<td>Every 3–5 years after age 10</td>
<td>Yearly after age 10 to 50 years of age.</td>
</tr>
<tr>
<td>LVNC</td>
<td>Every 3 years beginning in childhood</td>
<td>Yearly in childhood; every 1–3 years in adults.</td>
</tr>
<tr>
<td>RCM</td>
<td>Every 3–5 years beginning in adulthood</td>
<td>Yearly in childhood; every 1–3 years in adults.</td>
</tr>
</tbody>
</table>

UI Cardiovascular Genetics Program

- Clinical cardiovascular genetics program:
  - Outpatient clinics by disease
  - Hypertrophic Cardiomyopathy Association Center of Excellence
  - Inpatient consultation
  - Genetic counseling, genetic testing, family screening

- Research: identifying new genes and mutations:
  - Probands, families

- In-house genetic testing:
  - Pharmacogenetics, genetic panels
  - Iowa Institute for Human Genetics
Services Offered

- Imaging (echocardiogram, cardiac MRI, cardiac CT, MR or CT angiogram)
- Exercise stress testing
- Consultation with genetic cardiologist (MD and ARNP)
- Consultation with genetic counselor
- Additional evaluations as needed (consultants)
  - Cardiac electrophysiology
  - Interventional cardiology
  - Surgery, sleep medicine, psychiatry, neuromuscular,
- Genetic testing
- Research protocols
Some Genetic Testing Laboratories

- NIH Supported Website: [www.genetests.org](http://www.genetests.org)
- Ambry Genetics [www.ambrygen.com](http://www.ambrygen.com)
- Iowa Institute of Human Genetics (University of Iowa) [www.medicine.uiowa.edu/humangenetics/clinical/](http://www.medicine.uiowa.edu/humangenetics/clinical/)
Selected References

- Ackerman MJ et al. HRS/EHRA expert consensus statement on the state of genetic testing for the channelopathies and cardiomyopathies. Heart Rhythm 2011;8:1308-34.
- ACCSAP