Hypertrophic and Dilated Cardiomyopathy

Rahul Deo, MD PHD
Assistant Professor
Division of Cardiology, UCSF
Principal Investigator, CVRI
• Definitions
• Epidemiology: the scope of the problem
• Genetics
• Disease Course: Symptoms and Complications
• Therapies
  • established
  • emerging
The Scope of Heart Failure

• 660,000 new cases a year
• 5 million total patients in the United States
• Most common discharge diagnosis among hospitalized patients 65 and older
• 30 billion spent
• 5-year survival after diagnosis is worse than most cancers (i.e. once symptoms develop)
The Inherited Cardiomyopathies

- **Dilated Cardiomyopathy (DCM):** characterized by enlarged heart (ventricle) and reduced pumping function
- **Hypertrophic cardiomyopathy (HCM):** characterized by unexplained abnormal thickening of the heart
Dilated Cardiomyopathy
Epidemiology and Genetics

• affects 1:2500 people

• inheritance is typically autosomal dominant:
  50% risk of 1st degree relative being affected

• non-genetic causes include viral infection, drug toxicity, autoimmune disease
The Genetic Basis of DCM

>50 genes underlie DCM
- the overlap with other cardiomyopathies is substantial
- genes underlie cardiac structure and electrical activity
The Clinical Use of Genetics

• helps identify at risk individuals (screening)
• limited incorporation into clinical decision making: e.g. implantation of defibrillator even if heart pumping function is normal
• may one day be used to select individuals for molecular therapies
Cascade Screening Using Genetics

PKP2 R79X

Test 1st degree relatives

Test 1st degree relatives of mutation +
Disease Course

- **presentation**: usually shortness of breath (unless picked up incidentally on ECG or echocardiogram)
- **complications**: heart failure, arrhythmias, stroke
- **wide variability in disease severity**, arguing for other contributing factors
- **if you have autoimmunity** in your family (lupus, rheumatoid arthritis, etc.,) and have a cardiomyopathy (DCM, ARVC) please send me an email at rahul.deo@ucsf.edu.
Current Therapies: Typical Heart Failure Therapies Once Ejection Fraction is Reduced

- beta-blocker
- ACE-Inhibitor or Angiotensin Receptor Blocker
- Aldosterone antagonist
- ICD if reduced ejection fraction (or ventricular tachycardia resulting in fainting or cardiac arrest)

Unclear if introducing these in mutation + individuals helps
Emerging Therapies

• Valsartan/Sacubitril (LCZ696): dual acting angiotensin receptor-neprilysin inhibitor

• Trials:
  • ARRY-371797: LMNA-related dilated cardiomyopathy (Phase II)
  • Eteplirsen: Duchenne Muscular Dystrophy (DMD, Phase IIb)
Cardiomyopathy/Channelopathy Genes Where Truncating Mutations are Commonly Found

- DCM
- MYPN
- BAG3
- TTN
- LMNA
- ABCC9
- EMD
- EYA4
- FHL1
- SGCD
- TAZ
- DMD

- HCM
- (AND MIMICS)
- MYBPC3
- GLA
- LAMP2

- ARVC
- PKP2
- DSP
- DSC2
- DSG2

- Full-Length Protein

- Long QT Syndrome
  - KCNQ1
  - KCNH2
  - SCN5A

- CPVT
- CASQ2
- TRDN

Truncated Protein
Emerging Strategies for Treating Truncating Mutations: Lessons from Muscular Dystrophy
### Emerging Strategies for Treating Truncating Mutations: Lessons from Muscular Dystrophy

#### Table 1: Clinical trials using genetic therapies for Duchenne’s muscular dystrophy

<table>
<thead>
<tr>
<th>Drug name</th>
<th>Description</th>
<th>Company</th>
<th>Delivery route</th>
<th>Results to date</th>
<th>Current stage</th>
<th>Clinical trial number and/or URL*</th>
<th>Refs</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Viral gene therapy</strong></td>
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<tr>
<td>Biostrophin</td>
<td>rAAV2.5-CMV mini-dystrophin (d3990)</td>
<td>Asklepios Biopharmaceutical</td>
<td>IM (biceps)</td>
<td>Failed to establish long-term dystrophin expression; immune response against transgene in 4 out of 6 patients</td>
<td>Phase I (completed)</td>
<td><a href="http://www.askbio.com">http://www.askbio.com</a></td>
<td>11</td>
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<tr>
<td><strong>Termination codon read-through</strong></td>
<td></td>
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<tr>
<td>Ataluren</td>
<td>Nonsense suppression</td>
<td>PTC Therapeutics</td>
<td>Oral</td>
<td>Slowed loss of walking ability in patients with DMD or BMD (n = 174) at the lower of two doses tested</td>
<td>Phase III</td>
<td>NCT01557400; <a href="http://www.ptcbio.com">http://www.ptcbio.com</a></td>
<td>17, 49</td>
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<tr>
<td><strong>Exon skipping</strong></td>
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<tr>
<td>Eteplirsen (AVI-4568)</td>
<td>PMO morpholino targeting exon 51</td>
<td>Sarepta Therapeutics</td>
<td>IV</td>
<td>Well-tolerated and restored dystrophin expression in 7 out of 19 patients in a dose-dependent manner (&lt;20% normal levels)</td>
<td>Phase II</td>
<td>NCT00844597; <a href="http://www.sareptatherapeutics.com">http://www.sareptatherapeutics.com</a></td>
<td>22, 24</td>
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<tr>
<td>GSK2402968 (PRO051); Drisapersen</td>
<td>2’OMePS AON targeting exon 51</td>
<td>Prosensa–GlaxoSmithKline</td>
<td>SC</td>
<td>Restored dystrophin expression in 10 out of 12 patients (&lt;20% normal levels)</td>
<td>Phase III</td>
<td>NCT01480245; <a href="http://www.gsk.com">http://www.gsk.com</a>; <a href="http://www.prosensa.eu">http://www.prosensa.eu</a></td>
<td>23, 25</td>
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<tr>
<td>PRO044</td>
<td>2’OMePS AON targeting exon 44</td>
<td>Prosensa</td>
<td>SC or IV</td>
<td>Study ongoing</td>
<td>Phase I/IIa</td>
<td>NCT01037309</td>
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<tr>
<td><strong>Increasing levels of utrophin</strong></td>
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<tr>
<td>SMT-C1100</td>
<td>U�폰 modulator</td>
<td>Summit PLC</td>
<td>Oral</td>
<td>Safe, well-tolerated, achieved plasma levels shown to increase utrophin in DMD patient cells in vitro</td>
<td>Phase I (completed)</td>
<td><a href="http://www.summitplc.com">http://www.summitplc.com</a></td>
<td>42</td>
</tr>
</tbody>
</table>
Hypertrophic Cardiomyopathy
Epidemiology and Genetics

• affects 1:500 people

• inheritance is typically autosomal dominant: 50%
  risk of 1st degree relative being affected

• no clear non-genetic causes, though upper septal
  hypertrophy (angulated septum) seen in older
  individuals
The Genetic Basis of HCM

>12 genes underlie HCM

- the overlap with other cardiomyopathies is substantial
- ~50-60% yield of genetic testing
The Clinical Use of Genetics

• helps identify at risk individuals (screening)
• limited incorporation into clinical decision making:
• may one day be used to select individuals for molecular therapies
Disease Course

• **presentation:** usually shortness of breath (unless picked up incidentally on ECG or echocardiogram)

• **complications:** heart failure, arrhythmias, stroke

• **wide variability in disease severity,** arguing for other contributing factors (e.g. multiple mutations, high blood pressure)
Current Therapies: Focused on Reducing Contraction

- beta-blocker
- calcium channel blocker
- disopyramide
- ICD if risk of cardiac arrest
- septal myectomy or alcohol septal ablation if persistent symptomatic obstruction
An Updated Risk Score for Sudden Cardiac Death

HCM Risk-SCD Calculator

Age [Years] Age at evaluation

Maximum LV wall thickness [mm] Transthoracic Echocardiographic measurement

Left atrial size [mm] Left atrial diameter determined by M-Mode or 2D echocardiography in the parasternal long axis plane at time of evaluation

Max LVOT gradient [mmHg] The maximum LV outflow gradient determined at rest and with Valsalva provocation (irrespective of concurrent medical treatment) using pulsed and continuous wave Doppler from the apical three and five chamber views. Peak outflow tract gradients should be determined using the modified Bernoulli equation: Gradient= 4V^2, where V is the peak aortic outflow velocity

Family History of SCD

- No
- Yes History of sudden cardiac death in 1 or more first degree relatives under 40 years of age or SCD in a first degree relative with confirmed HCM at any age (post or ante-mortem diagnosis).

Non-sustained VT

- No
- Yes 3 consecutive ventricular beats at a rate of 120 beats per minute and <30s in duration on Holter monitoring (minimum duration 24 hours) at or prior to evaluation.

Unexplained syncope

- No
- Yes History of unexplained syncope at or prior to evaluation.

Risk of SCD at 5 years (%): 

ESC recommendation: 

http://doc2do.com/hcm/webHCM.html
Emerging Therapies

• Valsartan: Valsartan for Attenuating Disease Evolution In Early Sarcomeric HCM (VANISH, Phase II)

• MYK-461: Phase I trial (Myokardia)
Summary

• advances in potential treatments for heart failure, specific genetic disorders and HCM
• an updated risk score calculator for sudden cardiac death - still could be more accurate
• slow pace of new causal genes being added - probably many people have small contributions from a number of genes