Genetics in Cardiomyopathy

Prof Chris Semsarian
MBBS PhD MPH

No Disclosures
Inherited Heart Diseases

**Cardiomyopathy**
- HCM, DCM, RCM, ARVC, LVNC

**Congenital**
- e.g. ASD, TOF, myxomas

**Vascular**
- e.g. Marfan, Ehler-Danlos IV

**Arrhythmia**
- e.g. LQTS, CPVT, Brugada, SQT

**Metabolic**
- e.g. FH, homocystinuria

**Inherited Heart Diseases**
Common Features of Inherited Cardiomyopathies

- Autosomal dominant inheritance
- Generally younger, often asymptomatic
- Clinical diversity – no symptoms to sudden death
- Genetically heterogeneous, i.e. many genes
- Specialised multidisciplinary clinic approach
1. Hypertrophic Cardiomyopathy
Hypertrophic Cardiomyopathy

- **Prevalence** up to 1:200 (Semsarian et al, JACC, 2015)

- **Clinical heterogeneity** - no symptoms to dyspnoea, syncope, sudden death

- **LV hypertrophy**, diastolic dysfunction, LVOT obstruction, AFib, VT, **heart failure**

- Important **structural** cause of **sudden death**, including competitive athletes
Genetic Basis of HCM

**Sarcomere genes (top 5)**

- β-myosin heavy chain (MYH7)
- Myosin-binding protein C (MYBPC3)
- α-tropomyosin (TPM1)
- Cardiac troponins (TNNT2, TNNI3)

Pick up rate ~35-40% (>60% if Fam Hx)

**Figure 1**

HCM Landmarks

Maron, Maron, Semsarian. J Am Coll Cardiol, 2012
Identification of “HCM Phenocopies”

- Expanded genetic testing identifies **HCM phenocopies**
  - Glycogen storage (PRKAG2)
  - Fabry disease (GLA)
  - Danon disease (LAMP2)
  - Amyloidosis (TTR)

- Targetted management and therapeutic options, e.g.
  enzyme replacement

Perry Elliott, ESC 2014
2. Familial Dilated Cardiomyopathy
Familial Dilated Cardiomyopathy

- 15-30% of DCM familial
- Dilated cardiac chambers with impaired systolic function
- Presentation with heart failure, arrhythmias, sudden death
- Treatment involves lifestyle factors, pharmacotherapy, device therapies, surgery
### Genetic Basis of Familial DCM

#### 15-30% of DCM familial

<table>
<thead>
<tr>
<th>LOCUS</th>
<th>GENE</th>
<th>PROTEIN</th>
</tr>
</thead>
<tbody>
<tr>
<td>1p1-q21</td>
<td>LMNA</td>
<td>Lamin A/C</td>
</tr>
<tr>
<td>1q32</td>
<td>TNTT2</td>
<td>Cardiac troponin T</td>
</tr>
<tr>
<td>1q42-q43</td>
<td>RYR2</td>
<td>Cardiac RyR2</td>
</tr>
<tr>
<td>1q42-q43</td>
<td>ACTN2</td>
<td>α-actinin 2</td>
</tr>
<tr>
<td>2q31</td>
<td>TTN</td>
<td>Titin</td>
</tr>
<tr>
<td>2q35</td>
<td>DES</td>
<td>Desmin</td>
</tr>
<tr>
<td>3p21-p14</td>
<td>TNNC1</td>
<td>Cardiac troponin C</td>
</tr>
<tr>
<td>3p21</td>
<td>SCN5A</td>
<td>Cardiac Na⁺ channel</td>
</tr>
<tr>
<td>5q33</td>
<td></td>
<td></td>
</tr>
<tr>
<td>6q22</td>
<td></td>
<td></td>
</tr>
<tr>
<td>10q22-q23</td>
<td></td>
<td></td>
</tr>
<tr>
<td>11p11</td>
<td></td>
<td></td>
</tr>
<tr>
<td>11p15</td>
<td></td>
<td></td>
</tr>
<tr>
<td>12p12</td>
<td></td>
<td></td>
</tr>
<tr>
<td>12q22</td>
<td></td>
<td></td>
</tr>
<tr>
<td>14q12</td>
<td></td>
<td></td>
</tr>
<tr>
<td>14q12</td>
<td></td>
<td></td>
</tr>
<tr>
<td>15q14</td>
<td></td>
<td></td>
</tr>
<tr>
<td>15q22</td>
<td></td>
<td></td>
</tr>
<tr>
<td>17q12</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Pick-up rate 25-40%**
Role of Titin in Other Cardiomyopathies

Postpartum Cardiomyopathy

Alcoholic Cardiomyopathy


Ware et al. *J Am Coll Cardiol*, 2018
3. Arrhythmogenic RV Cardiomyopathy
Phenotype of Arrhythmogenic RV Cardiomyopathy (ARVC, ARVD, ACM)

Exercise Increases Age-Related Penetrance and Arrhythmic Risk in Arrhythmogenic Right Ventricular Dysplasia/Cardiomyopathy—Associated Desmosomal Mutation Carriers

Cynthia A. James, ScM, PhD, Aditya Bhonsale, MD, Crystal Tichnell, MGC, Brittnay Murray, MS, Stuart D. Russell, MD, Hanzikrishna Tandri, MD, Ryan J. Tedford, MD, Daniel P. Judge, MD, Hugh Calkins, MD
Genetic Basis of ARVC: The Desmosome

Pick-up rate 40-50%
Majority in \textit{PKP2} gene
# Clinical Phases of ARVC

<table>
<thead>
<tr>
<th>Phase</th>
<th>Clinical Features</th>
</tr>
</thead>
<tbody>
<tr>
<td>“Concealed” Phase</td>
<td>Asymptomatic, mild or absent RV features, Risk of sudden death event</td>
</tr>
<tr>
<td>Overt Electrical Disorder</td>
<td>Symptomatic RV arrhythmias, Overt RV functional and structural changes</td>
</tr>
<tr>
<td>RV Failure</td>
<td>Progressive loss of RV myocardium, Global RV dysfunction</td>
</tr>
<tr>
<td>Bi-ventricular Failure</td>
<td>Significant LV involvement, Bi-ventricular heart failure</td>
</tr>
</tbody>
</table>
Concealed ARVC in Sudden Unexplained Cardiac Death Events

Four families with sudden death events with overt structurally normal hearts with loss-of-function PKP2 variants!

Ingles et al. Circ Genom Prec Med, 2018
4. Left Ventricular Noncompaction
LV Noncompaction Cardiomyopathy (LVNC)

- **Familial** and **isolated** cases with variable age of presentation (children vs adults)

- Associated with other **cardiomyopathies**, e.g. HCM, DCM, and in physiological states such as in **athletes** or during **pregnancy**

- Complications include arrhythmias, heart failure, sudden death

- “True” genetic cause in < 10%
A systematic review and meta-analysis of the prevalence of left ventricular non-compaction in adults

Samantha B Ross¹,², Katherine Jones¹, Bianca Blanch¹, Rajesh Puranik²,³, Kevin McGeechan⁴,⁵, Alexandra Barratt⁴,⁵, and Christopher Semsarian¹,²,³,⁵,⁶

- No diagnostic gold standard
- Overdiagnosis partly due to switch to CMR imaging
- Unclear phenotypes...
- Genetic testing limited...

Echo ~ 1% MRI ~15%
Whole Genome Sequencing Improves Outcomes of Genetic Testing in Patients With Hypertrophic Cardiomyopathy

Richard D. Bagnall, PhD, Jodie Ingles, MPH, PhD, Marcel E. Dinger, PhD, Mark J. Cowley, PhD, Samantha Barratt Ross, BMedSci, André E. Minoche, PhD, Sean Lal, MBBS, PhD, Christian Turner, MBBS, Allison Colley, MBBS, MMedSc, Sulekha Rajagopalan, MBBS, Yemima Berman, MBBS, PhD, Anne Ronan, MRCP, MEd, Diane Fatkin, MBBS, Christopher Sensmar, MBBS, PhD, MPH

ABSTRACT

BACKGROUND Whole genome sequencing (WGS) is a comprehensive genetic testing approach that reports most types of nucleotide variants.

OBJECTIVES This study sought to assess WGS for hypertrophic cardiomyopathy (HCM) in which prior genetic testing did not establish a molecular diagnosis, and as a first-line genetic test.

METHODS WGS was performed on 58 unrelated patients with HCM, 14 affected family members, and 2 unaffected parents of a severely affected proband. The authors searched for nucleotide variants in coding regions of 184 candidate cardiac hypertrophy genes. They also searched for nucleotide variants in deep intronic regions that alter RNA splicing, large genomic rearrangements, and mitochondrial genome variants. RNA analysis was performed to validate splice-altering variants.

RESULTS The authors found a pathogenic or likely pathogenic variant in 9 of 46 families (20%) for which prior genetic testing was inconclusive. Three families had variants in genes not included in prior genetic testing. One family had a pathogenic variant that was filtered out with prior exome sequencing. Five families had pathogenic variants in noncoding regions, including 4 with deep intronic variants that activate novel splicing, and 1 mitochondrial genome variant. As a first-line genetic test, WGS identified a pathogenic variant in 5 of 12 families (42%) that had not received prior genetic testing.

CONCLUSIONS WGS identified additional genetic causes of HCM over targeted gene sequencing approaches. Extending genetic screening to deep intronic regions identified pathogenic variants in 9% of gene-elusive HCM. These findings translate to more accurate diagnosis and management in HCM families. (J Am Coll Cardiol 2018;72:419-29) © 2018 by the American College of Cardiology Foundation.
Whole Genome Sequencing in HCM

- Deep intronic variants and alternate splicing, mitochondrial mutations
  - WGS adds up to 15% pick up over panels and exomes

---

Bagnall et al, J Am Coll Cardiol, 2018
Take Home Messages

Genetic cardiomyopathies encompass many pathologies and are most commonly autosomal dominant

Family history and detailed phenotype assessment essential

Genetic testing is valuable in diagnosis, particularly in predictive testing of relatives

Specialised multidisciplinary clinic optimal approach to care

Major advances in genetic technologies will lead to greater understanding of inherited cardiomyopathies
Acknowledgements

Molecular Cardiology Program
University of Sydney, RPAH, Centenary Institute

Collaborators
National
International

Funding Bodies

@CSHeartResearch
Thank you

@CSHearResearch

chrissemsarian.com