The Genetics and Genomics of Familial Heart Disease
Bringing Precision Medicine to Life!

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Joint Appointment, Division of Cardiovascular Medicine
The Ohio State University Wexner Medical Center

No conflicts, nothing to disclose

I. The Explosion of Human Genetics and Genomics
II. What is Familial Heart Disease?
   • Mendelian (heritable) vs Complex (non-Mendelian) heart disease
III. What you need to know about a genetic evaluation
   • What is a genetic evaluation?
   • Common conditions needing genetic evaluation
   • Rationale for genetic evaluation
   • Molecular genetic testing
   • Results interpretation and return
   • Cascade clinical screening and molecular testing for families
IV. A Case Presentation of Dilated Cardiomyopathy
V. Discussion

The Explosion of Human Genetics and Genomics in Clinical Practice
Driven by high throughput sequencing
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**The Explosion of Human Genetics and Genomics in Clinical Practice**

Driven by high throughput sequencing

- 10 years ago – challenging to routinely sequence anyone
- 5 years – 2-3 genes possible (HCM 5 – 8 genes)
- 3 years – gene panels emerging (5-20 genes)
- 2 years – larger panels (10-40; pan-cardio – 76)
- 1 year ago – clinical exome emerges
  - exome = 19,000 – 20,000 genes encoding proteins

- Now – selective clinical exome sequencing:
  - 3 or more affecteds
  - negative panel
  - insurance coverage

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**Common terminology of genetic variation**

Categories of Genetic Variation:

- Nucleotide: single nucleotide polymorphism (SNP), single nucleotide variant (SNV)
- Genome organization: copy number variation (CNVs), inversions, deletions, translocations
- Epigenetics: changes in the regulation of gene activity/expression that are not dependent on gene sequence (e.g., methylation, retrotransposons)

**Genetic Variation - Nucleotide**

Frequency

- Common: > 5% of the population
- Rare < 1%, <0.5% of the population
- Very Rare <0.1%, <0.01%
- Observed one time, 'private' mutation

Type

- Synonymous (no change in amino acid)
- Missense (amino acid changed)
- Nonsense (stop codon)
- Short Insertions/Deletions
- Splice Site
- Truncating variants – nonsense, indels, splice site
- Terminology: 'mutation' versus ‘variant’
Familial Heart Disease is usually ‘Mendelian’

- Usually familial
- Usually identifiable pattern of inheritance (e.g., autosomal dominant, recessive, X-linked)
- Usually one gene
- Usually rare variants causal

Complex disease
- No discernable pattern of inheritance
- Uncommonly familial (1-2%)
- Many genes involved, common variants each with minimal impact
- Hypertension, diabetes, coronary artery disease

Mendelian Inheritance

- Classic Mendelian Inheritance
  - Autosomal Dominant
  - Autosomal Recessive
  - X-linked (dominant / recessive)

- Mitochondrial

Mendelian Inheritance - Autosomal Dominant
Other Types of Genetic Variation

Chromosomal abnormalities
• Translocations
• Duplications
• Deletions

Epigenetics: heritable changes in gene expression with no underlying changes in gene sequence
• gene methylation
• transcriptionally competent retrotransposons
• others

Epigenetic Variation in an Isogenic Strain


Genetic Evaluation: Purpose, Timing

The purpose of a genetic evaluation is to:
• Assess genetic risk
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• Assess genetic risk
• Provide a rationale and a plan of action to deal with it

This is especially relevant:
• In unaffected at-risk relatives
• If history of early death or significant morbidity (e.g., sudden cardiac death, myocardial infarction, heart failure, aortic rupture, etc)
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- For timely drug/device intervention

**Components of a genetic evaluation**

- Comprehensive family history

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- For timely drug/device intervention

Timing: A genetic evaluation is indicated with a new diagnosis of cardiomyopathy (DCM, HCM, ARVC, restrictive), channelopathy, aortopathy, dyslipidemia/premature coronary artery disease.

**Components of a genetic evaluation**

- Comprehensive family history
- Counseling about the condition:
### Components of a genetic evaluation

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### Components of a genetic evaluation

Genetic testing, if feasible and indicated:
- If positive, return of results
- If positive, cascade genetic testing of relatives
- If negative, consider exome sequencing if 3 or more affecteds, or if trio for possible *de novo* or recessive

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Recommend baseline clinical screening of at-risk relatives
Components of a genetic evaluation

Genetic testing, if feasible and indicated:
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- If positive, cascade genetic testing of relatives
- If negative, consider exome sequencing if 3 or more affecteds, or if trio for possible de novo or recessive

Recommend baseline clinical screening of at-risk relatives
Periodic clinical rescreening of at-risk relatives

Guidelines and Other Information Sources
Genetic Evaluation of Cardiovascular Disease
Guidelines:
- Cardiomyopathies – Heart Failure Society of America, 2009; Heart Rhythm Society, 2011
- Channelopathies – Heart Rhythm Society, 2011

GeneReviews (online NCBI/NLM resource)
- Hypertrophic Cardiomyopathy – Cirino, Ho
- Arrhythmogenic Right Ventricular Cardiomyopathy – McNally, McLeod, Dellefave-Castillo
- Thoracic Aortic Aneurysms and Dissection – Milewicz, Regalado
- Dilated Cardiomyopathy – Hershberger, Morales
- Catecholaminergic Polymorphic Ventricular Tachycardia – Napolitano, Priori, Bloise
- Brugada Syndrome – Brugada, Campuzano, Brugada
- ... and others

Indications for a Cardiovascular Genetic Evaluation

- New diagnosis of a known genetic condition with or without a positive family history
  - Cardiomyopathy
  - Channelopathy
  - Aortopathy
  - Familial Hypercholesterolemia, severe hyperlipidemia

- Clear family history of a morbid or lethal phenotype: sudden death, cardiomyopathy, aneurysm, pacemakers, bleeding, clotting, stroke, early myocardial infarction

Rationale for Genetic Referral, Genetic Testing, in Cardiovascular Genetic Medicine

Pre-symptomatic diagnoses enables:
- Improved surveillance for disease presentation
- Early treatment to decrease morbidity and mortality

By:
- Preventing disease progression (drugs, specific Rx)
- Improved timing of interventions (drugs, devices)
- Averting heart failure and arrhythmic events

Burkett, Hershberger, J Am Coll Cardiol 2005; 45:969-81
Hershberger, J Cardiovasc Trans Research, 2008;1:137-43
Hershberger, Morales, Siegfried, Genetics In Med 2010;12:655-667
Hershberger, Siegfried, J Am Coll Cardiol 2011; 57: 1641-49
### Disorders with Genetic Testing Available

<table>
<thead>
<tr>
<th>Cardiomyopathies</th>
<th>- DCM, HCM, RCM, ARVC, LVNC</th>
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<td>Channelopathies</td>
<td>- Long QT, Short QT, Brugada, CPVT (catecholaminergic polymorphic ventricular tachycardia), Timothy syndrome, others</td>
</tr>
<tr>
<td>Aortopathies</td>
<td>- Marfan, Loeys-Dietz, Thoracic Aortic Aneurysm and Dissection (TAAD), others</td>
</tr>
<tr>
<td>Familial Hypercholesterolemia (FH); other heritable lipid disorders</td>
<td></td>
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<tr>
<td>Pulmonary Hypertension, congenital heart disease, others</td>
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### Rules of the Road for Genetic Testing

- Phenotypes follow gene ontologies – inform test selection
- Mutations -- almost always unique to a pedigree - ‘private’ – make interpretation challenging
- Most genes have mutations scattered throughout coding sequence – entire genes need to be sequenced
### HCM Gene Ontology

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<tr>
<td>Sarcomere</td>
</tr>
<tr>
<td>MYBPC3</td>
</tr>
<tr>
<td>TNNT2</td>
</tr>
<tr>
<td>TNNC1</td>
</tr>
<tr>
<td>TNX3</td>
</tr>
<tr>
<td>TPM1</td>
</tr>
<tr>
<td>ACTC</td>
</tr>
<tr>
<td>MYL2</td>
</tr>
<tr>
<td>MYL3</td>
</tr>
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### Hypertrophic Cardiomyopathy

**Hypertrophic cardiomyopathy is a genetic disease of sarcomeric proteins**

- **MYBPC3** (myosin binding protein C) - 40%
- **MYH7** (beta myosin heavy chain) - 40%
- **TNNT2** (troponin T, others) - 10-15%

**Awad, Calkins, Judge, Nature Clinical Practice Cardiovascular Medicine 2008;5:258-267**

### Arrhythmogenic Right Ventricular Cardiomyopathy (ARVC) is a genetic disease of the desmosome

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<td>Desmosome</td>
</tr>
<tr>
<td>PKP2</td>
</tr>
<tr>
<td>DSG2</td>
</tr>
<tr>
<td>DSP</td>
</tr>
<tr>
<td>TNX3</td>
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**Awad, Calkins, Judge, Nature Clinical Practice Cardiovascular Medicine 2008;5:258-267**
Dilated Cardiomyopathy is a genetic disease of diverse protein function that yields a final phenotype:

- **TTN**: ~20%
- **LMNA**: 5-8%
- **MYH7**: 4%
- **MYPN**: 3.5%
- **TNNT2**: 3%
- **SCN5A**: 3%
- **BAG3**: 3%
- **MYPBC3**: 3%
- and many others.

Channelopathy Gene Ontology

Gene ontology for Channelopathies

**Long QT**
- KCNQ1 (LQT1) 30-35%
- KCNH2 (LQT2) 25-40%
- SCN5A (LQT3) 5-10%

**Catcholaminergic Polymorphic Ventricular Cardiomyopathy**
- RYR2 60%

**Brugada Syndrome**
- SCN5A (20-30%)
Additional comments on molecular genetic testing and counseling

Always start with the family member with the clearest and most compelling phenotype for testing

Genetic counselors:

• Obtain an extended family history
• Discuss heritability
**Additional comments on molecular genetic testing and counseling**

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- Obtain an extended family history
- Discuss heritability
- Coordinate testing and communicate results

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<th>Sensitivity</th>
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<td>DCM</td>
<td>30-40%</td>
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<tr>
<td>HCM</td>
<td>50-75% if familial; 30-40% sporadic</td>
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<tr>
<td>ARVC</td>
<td>~50%</td>
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<tr>
<td>Long QT</td>
<td>75%</td>
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Testing cost is a one-time event
- Many insurers now cover genetic testing
- Test panels are rapidly expanding at same cost

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**Additional comments on molecular genetic testing and counseling**

Always start with the family member with the clearest and most compelling phenotype for testing

**Genetic counselors:**
- Obtain an extended family history
- Discuss heritability
- Coordinate testing and communicate results
- Patient/family follow up especially for cascade evaluation, testing
- Information regarding test sensitivity:
  - DCM – 30-40%
  - HCM – 50-75% if familial; 30-40% sporadic
  - ARVC – ~50%
  - Long QT – 75%
Patient Case 1: MJ

This 36 year old Caucasian female had new onset of Idiopathic Dilated Cardiomyopathy in 2009 at 31 years of age

- Symptom onset for a few weeks, without obvious trigger
- Echo: 7.2 cm LVEDD, EF 10-15%
- ECG: LBBB, 144 msec; PR 134 msec; LAD
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- Echo: 7.2 cm LVEDD, EF 10-15%
- ECG: LBBB, 144 msec; PR 134 msec; LAD
- Cardiac magnetic resonance: dilated LV, severe global hypokinesis, EF 19%; normal RV size, moderate RV systolic dysfunction; bialtrial enlargement; moderate MR; minimal midwall fibrosis with gadolinium; no iron overload.

Urgent/Emergent VAD placement August 2009
- Treated medically
- Did well, improved
Patient Case 1: MJ

Urgent/Emergent VAD placement August 2009
- Treated medically
- Did well, improved
- VAD explanted September 2010

Close, careful follow up since, with full medical therapy
- 2012: LVEDD 6.2 cm; January 2015: 5.8 cm, EF 30-35%

ECG August 2014: QRS 90 msec, LAFB, PR 174 msec, lat T abnl
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- peak MVO2 August 2011: 21.9 ml/kg/min

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- peak MVO2 August 2011: 21.9 ml/kg/min
- ICD in place, no shocks

The Genetics and Genomics of Familial Heart Disease
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Amy Sturm, LCGC
Associate Professor
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### MJ – Genetic testing results
(76 gene “Comprehensive Cardiomyopathy” panel)

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<th>MAF</th>
<th>CLIA lab's interpretation</th>
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<td>MYBPC3*</td>
<td>c.26-2A&gt;G</td>
<td>IVS1-2A&gt;G</td>
<td>0.01% (EA)</td>
<td>Disease-causing mutation</td>
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<tr>
<td>TNNC1^</td>
<td>c.446A&gt;G</td>
<td>Asp149Gly</td>
<td>0% (EA)</td>
<td>Variant, likely disease-causing</td>
</tr>
<tr>
<td>LAMA4~</td>
<td>c.4624A&gt;T</td>
<td>Asn1542Tyr</td>
<td>0.02% (EA)</td>
<td>Variant of unknown significance (VUS)</td>
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- ^Reported previously in association with HCM; destroys canonical splice acceptor site
- *Novel variant; non-conservative amino acid substitution; conserved position; missense variants in nearby residues have been reported in HGMD in association with CMP (E134D, D145E, I148V)
- ~Novel variant; semi-conservative amino acid substitution; position not well conserved; no nearby variants reported in HGMD in association with CMP

---

### MJ – Genetic testing results
(76 gene “Comprehensive Cardiomyopathy” panel)

Ordered targeted testing
76 gene Panel testing

### MJ – Genetic testing results
(76 gene “Comprehensive Cardiomyopathy” panel)

PPOM
Heart Transplant
VAD
NICM
Sudden Death
• The family is enrolled in our DCM Research Protocol.

• Our exome data suggests that multiple variants may be more common than previously thought.

  ➢ Which variants cause DCM and which act as modifiers?

• Our data also suggests that PPCM shares the same genetic basis with DCM.
### Research

- The family is enrolled in our DCM Research Protocol.
  - Our exome data suggests that multiple variants may be more common than previously thought.
    - *Which variants cause DCM and which act as modifiers?*
  - Our data also suggests that PPCM shares the same genetic basis with DCM.
    - *What is the molecular basis underlying pregnancy onset of DCM?*

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### Patient Case 2: JA

This 57 year old Caucasian male with ischemic cardiomyopathy, coronary artery disease treated at an outside hospital
- First stent 2005,  
- Clopedigrel stopped after 1 year, late in-stent thrombosis 2006, large MI, recovered to normal systolic function  
- 2006 restented; Clopedigrel again stopped, large MI 2007, EF 20%.

First OSU notes 2007  
- Echo 2007: LVEDD 6.7 cm, EF 16%  
- Cardiac MRI 2007: dilated LV, EF 23%; non-viable LAD territory; valves OK  
- Close, careful follow up, full medical therapy  
- Progressive disease
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- Progressive disease

Heart transplant December 2011, now doing well

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- ^Reported numerous times as VUS; has been present in ARVC patients with other variants
- ~Reported previously as VUS; reported in ARVC patient with other variant; conservative amino acid substitution; position not conserved

Variations on the Typical Mendelian Disease Paradigm Relevant to DCM

Management and Screening Recommendations

- Clinical screening of all first-degree relatives
- Segregation genetic testing in affected family members
- What about predictive testing?